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Risk factors of importance in the 21st century. Can they be controlled?

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SUMMARY

Among a number of risk factors for cancer identified from previous epidemiological and experimental studies, tobacco, diet and oncogenic viruses have been most important risk factors globally in the past and will remain the same in the 21st Century. Tobacco has been controlled successfully in some developed countries, but not yet so in some other countries. Methods of dietary intervention should be tailored depending on the dietary conditions in the country/community. Prevention of infection of oncogenic viruses is also important. Primary prevention of cancer is an effective and economical cancer control method.

INTRODUCTION

Marked geographical variations and time-trends of cancer incidence, as well as results of migrant studies suggest the importance of environmental factors in the etiology of cancer. Close correlations between specific cancers and some environmental factors such as dietary components and tobacco have also provided strong evidence of being environmental risk factors of cancer and new opportunities for cancer prevention. Previous analytical epidemiological and experimental studies have revealed several important risk factors for cancers of specific sites(Table 1).

Attributable risks for major risk factors have been estimated by Wynder & Gori[1], Doll & Peto[2] and several

Table 1 Risk factors of cancer and major sites of cancer to be affected

Risk factors	Major sites of cancer to be affected
Tobacco	Oro-pharynx, Larynx, Lung, Esophagus, Stomach, Pancreas Liver, Ureter, Bladder, Cervix
Diet	
Fat/calorie	Colon, Breast?, Prostate?
Dietary fiber*	Colon
Salt	Stomach
Vegetables/fruits*	Stomach and other organs
Infection	
HBV/HCV	Liver(HCC)
HPV/HSV-2	Cervix
EBV	Lymphatic system, Nasopharynx
HTLV-1	Hemato-lymphatic system(T-cells)
Parasites	Liver, Bladder
Reproductive factors	Breast
Occupation	Lung, Skin, Bladder
Alcohol	Oro-pharynx, Esophagus Colo-rectum?, Breast?
Sunlight/Radiation	Skin
Pollution	Lung
Medicine and medical procedures	Hematopoietic system
Sexual behavior	Cervix
Industrial products	
Food additives	
Obesity	Breast
Exercise*	Colon-sigmoid
Stress	Stomach

*Low risk(=protective)factor

other researchers. They unanimously indicate that attributable risks for tobacco and diet are outstandingly high accounting for about 60-70%. An attributable risk for oncogenic viruses may be relatively large in populations where liver cancer and cervical cancer are relatively common. Attributable risks for other risk factors are relatively low. Attributable risks for major risk factors of cancer today may not change appreciably in the 21st Century and those for tobacco and diet will still be outstandingly high.

CONTROLLABILITY OF MAJOR RISK FACTORS

Environmental risk factors are preventable to some extent if adequate measures are taken and much efforts are paid. Controllability of major risk factors for cancer may be as follows:

Tobacco: In several developed countries such as the USA, Canada, UK, Scandinavian countries, Denmark, Australia, Singapore, as the result of major prevention and control efforts, public health measures directed toward reducing smoking are succeeding and the prevalence of smokers have been markedly reduced especially in men, but in some other countries including Japan tobacco control is not yet successful and tobacco will still be a major risk factor of cancer in the 21st Century.

Betel: In some South-East Asian countries betel-chewing is a common habit and has been a major risk factor for oral cancer. Betel chewing can also be controlled by health education. The screening of oral cancer and its precancerous lesions is effective for early detection and provides a good opportunity for health education.

Diet: Excess intake of some food components such as fat, calorie, and salt and insufficient intake of some other food components such as dietary fiber, fresh vegetables and fruits elevate risks of some specific cancers. The impact of dietary intervention on cancer prevention may be large as has been estimated by Wynder & Gori[1] and Doll & Peto[2]. Methods of dietary intervention may vary from country to country depending on dietary habits and food processing methods. Chemoprevention has been tried to supply protective factors. It is also important to avoid excess intake of fat/calorie and salt. However, it is not easy to change dietary habits and food processing methods. Thus, diet will also remain to be a major risk factor of cancer in the 21st Century.

Infection: Some oncogenic viruses(HBV, HCV, HPVs, HSV-2, EBV, HTLV-1,etc) are major risk factors for some specific cancers such as liver cancer and cervical cancer, Burkitt lymphoma, nasopharyngeal cancer and adult T-cell leukemia/lymphoma(ATL)(Table 1). Some parasites such as schistosomiasis in the urinary bladder and liver and clonorchiasis in the bile duct are risk factors of bladder cancer and cholangiocarcinoma in some African and Asian countries. If adequate preventive measures against those oncogenic viruses and parasites are taken, they will eventually be controlled.

Reproductive factors: Early pregnancy, full term delivery, and lactation are protective factors for breast cancer. However, it may be difficult to modify these reproductive factors for the purpose of primary prevention of breast cancer. Dietary intervention avoiding excess intake of fat/calorie may be a more practical and effective method.

Occupation: Occupational exposures to aromatic amines, arsenic, asbestos, benzene, bischloromethyl ether, cadmium, chromium, ionizing radiation, isopropyl oil, mustard gas, nickel, polycyclic hydrocarbons(soot, tar,

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oil), ultraviolet light and vinyl chloride are risk factors for cancers of the bladder, skin, lung, marrow, prostate, bone, nasal sinus, larynx and liver[3]. Some of the occupational exposures have already been controlled to an acceptable level largely due to stringent regulations ,but some other occupational exposures remain to be controlled.

Alcohol: Excess alcohol consumption is a definite risk factor for cancers of the oro-pharynx, larynx, esophagus and a probable risk factor for cancers of the liver, colo-rectum and breast. Similar control measures as in smoking control may be applicable to alcohol control. However, complete avoidance of alcohol intake may be unnecessary and moderate drinking may be acceptable as the attributable risk to alcohol is estimated to be much smaller than that of smoking[2] and some beneficial effects of moderate drinking on total mortality have been implicated in a recent study[4].

Sunlight: Excess exposure to sunlight is a major risk factor of skin cancer in whites. Global efforts are needed to protect the ozone layer and health education is needed to avoid unnecessary exposure to sunlight.

Radiation: Exposure to ionizing radiation due to x-ray tests and inhalation of radon gas is regarded as a risk factor some cancers; leukemia, thyroid cancer, skin cancer and lung cancer. Effects of the Atomic bomb in Hiroshima and Nagasaki have been studied extensively for the last 50 years and effects of the Chernobyl nuclear power plant accident have been monitored. As the number of nuclear power plants has been increased all over the World, the safety of nuclear power plants will become more and more important in the future.

Pollution: Ambient air pollution in industrialized cities and indoor pollution in the kitchen in some countries such as China and Hong Kong may be associated with an increased risk of lung cancer, but more studies are needed to confirm the causal relation.

Medicine and medical procedures: Certain drugs such as alkylating agents, arsenic, chloromaphazine, estrogen(unopposed), immunosuppressive agents, phenacetin, etc. are proven to be carcinogenic in humans[5], but the attributable risk may be small.

Sexual behavior: Cancer of the cervix is associated with early sexual activity, especially with multiple partners. The human papilloma viruses(HPV16,18,33 etc.) and the herpes simplex virus(HSV-2) are possible cause of cervix cancer and could be passed between partners during intercourse. The attributable risk of those viruses may be large. Health and moral education is needed to prevent infection of those oncogenic viruses.

Industrial products: Some industrial products such as some specific types of herbicides, hair dyes and some other chemicals are suspected to be carcinogenic, but the attributable risk is estimated to be small.

Food additives: Some food additives are carcinogenic, but some others, such as antioxidative agents(BHT, carotene, vitamine C, etc.) may contribute to a decreased risk of cancer. In general, the overall attributable risk of food additives may be small.

Obesity: Obesity is associated with an increased risk of breast cancer, especially of postmenopausal breast cancer and endometrial cancer.

Exercise: The risk of colon-sigmoid cancer is reported to be elevated in sedentary workers. Thus, physical activity may be contributing to a decreased risk of colon cancer possibly through increased bowel movement.

Stress: Stress is reported to be associated with an increased risk of stomach cancer. More studies are needed to establish the causal relation and to estimate the attributable risk.

PREVENTABILITY OF CANCER

Although the risk of cancer attributable to environmental risk factors is estimated to be large; 70-90%, it is not necessarily possible to prevent them all. Greenwald & Sondik estimated proportions of reduction of cancer mortality in the USA by year 2000 by prevention, screening and treatment[6]. They estimated that 8% of cancer could be prevented by dietary control; fat reduction to 25% of total calories and fiber increase to 20-30g/day) and another 8(15)% of cancer could be prevented by smoking control; reduction in adults smoking prevalence if achieved in year 2000(1990). All together only 16(23)% of cancer could be prevented by dietary and smoking control, while Doll & Peto had estimated that diet and tobacco occupied 65% of cancer mortality in the USA[2]. I also estimated preventable fraction of cancer by primary prevention in Japan. The optimistic(realistic) estimate of preventable fraction was 8(4)% by smoking control if smoking rate is reduced to 30(50)% in male adults and 5(10)% in female adults, 12(6)% by improvement of dietary habits(restriction of salt intake and avoidance of excess intake of fat, etc.) and 6(3)% by prevention of HBV/HCV infection. All together, optimistically 26%(realistically 13%) of cancer may prevented if much efforts are paid to smoking control, improvement of dietary habits and prevention of HBV/HCV infection in Japan.

The preventable fraction of cancer and the methods of prevention may vary from country to country depending on the common cancer and their major risk factors in each counry.

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Problems in environmental oncology. Lessons learnt from the Chernobyl experience

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The long-term health effects of the Chernobyl accident are only now beginning to show. Much of the current evidence of health-related long-term after effects of environmental radiation emanates from the survivors of atomic bomb explosions. This work has been conducted after a delay of almost 50 years. The Chernobyl accident has produced a population affected by an environmental man-made catastrophy, and exposed to a different variety of radio-nuclides under very special conditions, which are not similar to those caused by the detonation of a nuclear weapon.

The various health consequences of the Chernobyl nuclear accident, which happened in April 1986, are still uncertain in spite of the very intensive study which has been undertaken during the past eight years. The lack of understanding of the nature of the effects from environmental exposure to ionizing radiation when vast areas are contaminated, and the difficulties which arise in estimating the actual population exposure, especially to short-lived isotopes, make the analysis of the oncological situation and any predictions for its further development very difficult.

In May 1991 the World Health Assembly endorsed the establishment of the International Programme on the Health Effects of the Chernobyl Accident (IPHECA), under the auspices of the World Health Organization, to study and facilitate mitigation of the harmful influence of the catastrophy on the health of the affected population. IPHECA is a cooperative effort between the three most affected countries - Belarus, the

The NCIC framework for cancer control planning

Advisory Committee on Cancer Control
(Chair: Dr. A.L.A. Fields)

National Cancer Institute of Canada

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SUMMARY

The National Cancer Institute of Canada (NCIC) has recently developed a new conceptual framework to assist in the planning of cancer control activities. The NCIC Framework includes the full range of cancer control activities including fund-raising, public education, patient services, cancer registries and research. It emphasizes partnerships, our mutual dependencies and our unifying commitment to reducing the burden of cancer.

The model classifies cancer control activities into five categories:

1) Fundamental Research
2) Intervention Research
3) Program Delivery
4) Surveillance and Monitoring
5) Knowledge Synthesis and Decision-making.

The Canadian Cancer Society (CCS) and the NCIC have used the Framework to plan conferences and workshops, to identify critical research gaps and priorities and to help formulate positions on contentious issues. It helps service delivery organizations ensure that their programs are soundly based on scientific evidence and promotes systematic program development and evaluation. Equally, it helps research organizations ensure that the limited funds available for intervention and program delivery research are directed appropriately and it emphasizes the dissemination of important new research findings into the community to benefit the whole population.

We believe that the NCIC Framework has wide applicability for any agency concerned with cancer control and that it can be easily modified to facilitate planning for other organizations concerned with health care, social services or research.

INTRODUCTION

Diminishing resources have intensified the need for systematic approaches to making decisions and setting priorities. The challenge is especially pertinent to cancer control: an aging population, unrelenting increases in incidence rates and a frustrating stability of mortality rates are compounding the problems faced by other parts of the health care system. Improved cancer control planning requires a framework within which to set priorities, allocate resources and review progress.

THE NCIC FRAMEWORK

The National Cancer Institute of Canada (NCIC) has defined cancer control broadly as follows: Cancer control is the identification, development, promotion, diffusion and delivery of effective and ethical methods of cancer prevention, screening and care services and programs for individuals and groups, always with their active participation. This definition reflects a vision of cancer control which encompasses all activities that contribute to reducing the burden of cancer for the individual and the population.

In developing the Framework we sought to: (A) use a common language applicable to the full range of cancer-control activities including programs such as fund-raising, volunteerism and advocacy as well as biomedical research and service delivery; (B) demonstrate the interrelationships between research, program delivery and surveillance; (C) promote a disciplined and systematic approach to synthesising existing knowledge and identifying the initiatives most likely to lead to a reduction in the burden of cancer; and, (D) incorporate societal values such as high ethical standards, participatory decision-making for patients, efficiency and public accountability.

Figure 1 shows the major components of the "NCIC Framework". Cancer control activities are displayed in five broad categories: "Fundamental Research", "Intervention Research", "Program Delivery", and "Surveillance and Monitoring" linked by the fifth category - Knowledge synthesis and Decision-making. All activities are governed by the four key principles - accountability, empowerment, ethics and efficiency.

THE CANCER CONTROL CATEGORIES

Activities categorized as Fundamental Research are designed to expand our knowledge of fundamental

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mechanisms that underpin effective cancer-control strategies. Fundamental Research answers the question: "What do we know?" All disciplines upon whose theories and research findings successful interventions, programs and policies can be based are included since advances in cancer control may derive from many disciplines.

Surveillance and Monitoring includes the collection, review and analysis of data describing the incidence, prevalence, morbidity, or mortality attributable to cancer and answers the question: "Where are we?" These data not only monitor our current performance they also generate testable hypotheses for fundamental research, intervention research and program delivery. The category of Intervention Research includes activities which assess the efficacy and effectiveness of any specific intervention designed to achieve specified outcomes and address the question: "What works?" Interventions commonly tested are those to be applied in diagnostic, therapeutic, educational, behavioural, sociological, and policy fields, but the techniques of intervention research can be applied even more broadly to include activities such as fund-raising and advocacy, which are increasingly critical to the cancer-control effort. Within the NCIC Framework, this category is subdivided into six stages (Figure 2). The first five stages are based on the model developed by the National Cancer Institute in the U.S. (1). The sixth stage - dissemination/adoption studies - recognizes the importance of research into the ways in which findings can be integrated into actual practice. Research on any particular intervention should proceed sequentially through the six stages.

The category of Program Delivery is concerned with the design and delivery of programs to systematically provide effective interventions to large groups or populations and addresses the question: "How should effective interventions be delivered?" Evaluation is an integral component of this activity.

The NCIC Framework identifies six stages for the development and implementation of programs to assist program planners to develop effective programs using a logical and orderly sequence which closely parallels the approach used to develop and disseminate effective interventions (Figure 2).

The distinction between Intervention Research and Program Delivery in the NCIC Framework is of practical importance. It recognizes that when an effective intervention is identified, it is not always necessary to deliver the intervention through a formal program. However, once it is determined that a formal program is required, a staged approach to program delivery ensures its systematic development.

Figure 2 provides a matrix which can be used to locate the stage of development of any particular intervention or program. For example, a synthesis of existing knowledge may lead to a conclusion that screening mammography for women aged 50-69 is at stage 6 of Intervention Research and stage 4 of Program Delivery while screening mammography for women aged 40-49 requires further Intervention Research at Stage 3.

Knowledge Synthesis and Decision-making is at the hub of the NCIC Framework and orchestrates activity in all other categories. The conclusions and recommendations that result answer the question: "What's next?" and promote evidence-based decisions to support work in one or more of the other four categories. This "filtering" process is critical in today's economic environment and should be used in an iterative manner whenever significant new information becomes available.

KEY PRINCIPLES

Around the boundary of the NCIC Framework are four key principles that should characterise all cancer control activities: accountability, empowerment, ethics, and efficiency (Figure 1).

Accountability is the acceptance of responsibility for one's own actions, including the need to report, explain or justify actions or conduct (2).

Empowerment is the acquisition, by individuals or groups, of the capacity to participate fully in decision-making processes equitably and fairly, with the recognition that such participation is, and is seen to be, legitimate (2).

Ethics are rules or principles that govern right conduct, including precepts relevant to scientific merit - on the premise that scientific merit is a prerequisite for ethical research and program delivery (2).

Efficiency is the extent to which benefits achieved are causally related to the costs and efforts expended, i.e., the extent to which unnecessary effort or waste is reduced or eliminated (3).

As applied to Fundamental Research, for example, these principles would help to ensure that investigators conduct their research efficiently and ethically, and that they are held accountable to the funding agencies and possibly other bodies for the conduct of their research. As applied to Program Delivery, these principles would be used to ensure that the proposed program meets stated ethical standards, empowers persons directly affected by the program, is undertaken in an efficient manner and is fully accountable to appropriate authorities and groups.

DISTINCTIVE FEATURES

The NCIC Framework has several distinctive features. First, it is designed to be highly inclusionary, linking the efforts of basic scientists, behavioural and social researchers, health care providers, policy makers, administrators, educators, epidemiologists, cancer registry staff, volunteers, fundraisers, and others engaged in the cancer control effort.

Second, it recognizes that the identification and dissemination of effective interventions as well as the design and delivery of effective programs should both

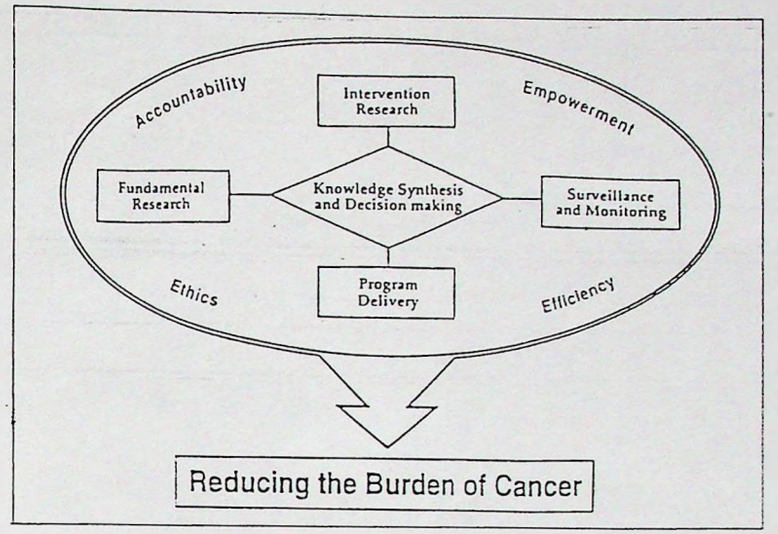

Figure 1

The NCIC Framework for Cancer Control showing the five categories into which all cancer control activities can be assigned, the four overarching principles and the unifying purpose of cancer control - to reduce the burden of cancer.

STAGES OF INTERVENTION RESEARCH	THEMES: Prevention	Screening	Diagnosis	Treatment	Rehabilitation	Palliation	Other	Fundraising	Public Education	Advocacy	STAGES OF PROGRAM DELIVERY
1. Hypothesis generation											1. Program Formulation
2. Methods development											2. Pre-testing
3. Efficacy trials											3. Pilot testing
4. Effectiveness trials (in a single defined population)											4. Implementation/ evaluation (in single defined population)
5. Implementation studies (in multiple defined populations)											5. Implementation/ evaluation (in multiple defined populations)
6. Dissemination/adoption											6. Full operation/ institutionalization

Figure 2

A Matrix for Intervention Research and Program Delivery listing the six stages for each category and selected subject themes which may be explored within either category.

proceed systematically through six similar but distinctive stages. The medical research community has recognized the need for the orderly development of interventions but has placed little emphasis on systematic program design and evaluation. By contrast, the health care delivery system including voluntary agencies such as the Canadian Cancer Society, have focused on program design and delivery with less emphasis on assessing the evidence for the effectiveness of the interventions delivered by the program. The NCIC Framework supports both parties in strengthening and balancing their cancer control efforts.

Third, the NCIC Framework recognizes the pivotal role of Knowledge Synthesis and Decision-making in the development of any cancer control initiative. New significant research findings or surveillance data should generate a review of "What do we know?" and a reconsideration of "What's next?". Review of the facts, and the perspectives of providers and consumers will help ensure that our resources are appropriately directed. It will help decision-makers delay widespread implementation of untested programs or immature technology and will stimulate research that defines and addresses the relevant question at the proper stage of the research continuum.

Fourth, the NCIC Framework identifies four principles that should underlie all cancer control activities. Those responsible for reviewing or approving research protocols, program plans or data collection activities should ensure that each principle has been appropriately incorporated into any cancer-control activity.

One of the most important benefits of the NCIC Framework is that it encourages those responsible for priority-setting and decision-making incorporate information derived from all areas of cancer control activity into their analysis and to organize their knowledge systematically. Critical gaps in knowledge can be identified and service delivery for priority attention. Use of the NCIC Framework will not provide easy solutions to controversial issues, rather, it disciplines the process of decision-making by ensuring that evidence from all areas is critically evaluated prior to embarking on new research or program initiatives.

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cancers were shown as flat lesions. The common types of mucosal cancers detected were 0-IIb type and 0-IIc type of lesions. 0-I type and 0-III type of lesions were mostly submucosal cancer even when small. Particularly, the 0-IIb (flat) type of lesion was more common in epithelial cancer and it was detected more easily by endoscopic staining with Lugol's solution than by the gross appearance. With Lugol's solution the normal epithelium of the esophagus stains dark brown while mucosa with pathologic changes remains unstained. Endoscopic staining with Lugol's solution was effective not only for screening examination of mucosal cancer, but also for confirming the exact extent of mucosal cancer. Malignancy in the basal layer of the epithelium or dysplasia was also demonstrated as an unstained area.

As for symptoms in patients of T1 cancer of the esophagus, a tingling sensation in the esophagus caused by food and a feeling of stenosis were the most common symptoms, followed by retrosternal pain. However, no symptoms were seen in 47% of patients. The diagnosis of esophageal cancer was occasionally made in the periodic checking.

When a lesion suspected to be mucosal cancer was less than 2cm x 2cm in size and the absence of lymph node metastasis was proved, endoscopic mucosal resection was indicated. Endoscopic mucosal resection was performed in 41 cases. Histologically these consisted of mucosal cancer in 30, submucosal cancer 4, dysplasia 5 and 2 unknown. As postoperative complications, a small fissure was seen in one case and stenosis in two cases and bleeding in three cases. But these were cured conservatively. The longest period of follow-up in cases of endoscopic resection was 4 years and 9 month, and no recurrence has been observed in any case.

In summary;

Endoscopic examination and the endoscopic staining with Lugol's solution was the most advisable method in diagnosis of early and minute cancer of the esophagus. As for the minimally invasive surgery of the esophageal cancer, endoscopic mucosal resection was common for lesions suspected to be mucosal cancer less than 2cm x 2cm in size, with no nodal involvement. The procedures and the clinical results of endoscopic mucosal resection of the esophagus are presented.

Strategies for primary prevention of cancer in developing countries

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SUMMARY

Methods for cancer prevention in developing countries should be inexpensive, practical and effective. Tobacco control and nutrition improvement, in particular frequent consumption of green-yellow vegetables (GYV), fit quite well to the criteria. Tobacco use, either by chewing or smoking, is undoubtedly the leading risk factor for cancer, while risks for cancer in daily consumers of GYV rich in beta-carotene and vitamins C have been shown to be one half or less. Hepatitis B vaccination programmes have already started in selected countries in Africa and Asia. Until vaccination for other cancers become also available, above stated life style modification must be the most effective strategies for cancer prevention in developing countries.

INTRODUCTION

It was estimated approximately 7.62 million new cancer cases in the world in 1985 fairly evenly shared between the developed and developing countries (Parkin et al, 1993)(1). Therefore in any worldwide cancer control programme, problems in developing countries should never be neglected in considering priority in cancer control programmes. Primary prevention is of particular importance in case of developing countries in view of limited resources available for early detection and diagnosis of cancer, not to speak of treatment. Strategies for cancer primary prevention should therefore be considered carefully selecting plans which are effective and still can be carried out with low cost.

MATERIALS AND METHODS

Considerations were given using results of numerous epidemiological studies on cancer in developing countries in the literature and also following monographs.

1. Cancer Incidence in Five Continents Vol. 1-6, UICC/IARC, 1966-1982.
2. Life-styles and Mortality, T. Hirayama, Karger, 1990.

FEATURES OF CANCER IN DEVELOPING COUNTRIES

Although principles of strategies for primary prevention of cancer should basically be same in both developed and developing countries, cancer patterns characteristic in developing countries must carefully be taken into consideration. Number one consideration should be focussed on the type of cancer particularly prevailing in developing countries. In sharp contrast to developed countries where cancers closely related to affluence in diet and other life-styles prevail, major cancers in high incidence in developing countries are more or less closely related to poverty, malnutrition and lower levels of cleanliness, e.g. cancers of esophagus, stomach and cervix. Tobacco related cancers prevail both in developed and developing countries. In developed countries, tobacco is used almost exclusively in the form of cigarette smoking. However somewhat different types of tobacco use also exist in developing countries such as tobacco chewing and/or bidi smoking as in India. Another feature of cancer in developing countries is the high prevalence of virus-related cancers, e.g. liver cancer (HBV, HCV), Burkitts lymphoma, nasopharyngeal cancer (EBV), cervical cancer, penile cancer (HPV), Kapposi sarcoma (HIV). Therefore special measures against such virus infection, e.g. vaccination, must seriously be considered in cancer control plan in developing countries.

CANCER PREVENTION PLAN IN DEVELOPING COUNTRIES

As in developed countries cancer prevention plan should carefully be made under following headings ;

Researchers plan ; (prevention strategies planned by basic researchers and by epidemiologists)
Communityy plan ; (prevention which is beyond individuals reach)
Individual plan ; (behavior change, life-style modification etc.)

Methods for cancer prevention in developing countries should be inexpensive, practical and effective. The method, first of all, should be not only effective in reducing cancer risk but also must be practical and cost effectiveness should be high. The method should be preferably effective for prevention of cancer of multiple sites, killing many birds by one stone. One may even doubt the possibility of the existence of such methods for primary prevention of cancer. Thanks to series of intensive basic and epidemiological research on cancer in man, such effective prevention methods which can easily be carried out in developing countries with surprisingly low cost are now available.

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Tobacco control and nutrition improvement, in particular frequent consumption of Green-Yellow Vegetables (GYV), fit quite well to the above mentioned criteria.

First, the evidence for the effectiveness and practicability of such combined strategy of tobacco control and nutrition improvement has been clearly shown by numerous epidemiological studies. Second, underlying basic mechanism explaining the effectiveness of such strategy has been already known. It has been shown that tobacco chewing and smoking results in continuous production of oxygen radicals while beta-carotene and vitamine C rich in GYV are believed to suppress such action of oxygen radicals as scavengers assisting SOD (superoxide dismutase) and other anti-oxidative enzymes.

TOBACCO CONTROL

Tobacco use, either by chewing or smoking, is undoubtedly the leading risk factor for cancers of mouth, pharynx, esophagus, stomach, liver, pancreas, lung, urinary bladder, cervix of uteri etc. Numerous case-control studies, and cohort studies conducted in Asia clearly demonstrated tobacco use is the primary risk determinant of cancer of many sites which prevail in each Asian country. For instance, tobacco chewing was identified as the leading risk factor of cancer of mouth and pharynx by series of case-control studies conducted in South East Asia (2). A large-scale census-population based prospective cohort study in Japan, in which 265,118 subjects age 40 and above residing in 6 prefectures representing whole country were followed up for 17 years, clearly showed cigarette smoking is by far the most important risk factor of cancer of most sites as listed above (3). Lung cancer risk was observed to be doubled by 2 cigarettes a day in line with other 8 cohort studies in the world (4). Risks tended to be higher the higher the dose and the longer the duration of smoking. Prevention of start of habit of tobacco use must be the best approach, followed by cessation of tobacco use. Cancer risk was observed to approach to the level of non users with the lapse of years after cessation of the habit.

The discovery of lung cancer risk elevation by passive smoking by our large scale cohort study (5) must be of particular importance in developing countries as the exposure to sidestream smoke is considered to be much higher since people live in small congested rooms. Numerous studies confirmed our observation of lung cancer risk elevation by household exposure to passive smoking. Risks were also high for nasal cancer, brain tumor and breast cancer (6). At any event the problem of passive smoking appear even more serious in developing countries.

NUTRITION IMPROVEMENT

Risks for cancer of most sites were observed to be much lower in daily consumers of GYV compared with non daily consumers (Hirayama, 1979)(7). Compared with non daily GYV consumers, risks for cancer of different sites were observed much lower in GYV daily consumers even for those smoking cigarettes daily, drinking alcohol daily and consuming meat daily (Fig. 1)(3). Such risk difference by GYV consumption was noted to become larger when compared by the amount of beta-carotene included in each GYV. When compared by the serum level of beta-carotene, largest risk difference was observed (Harris et al, 1991)(8).

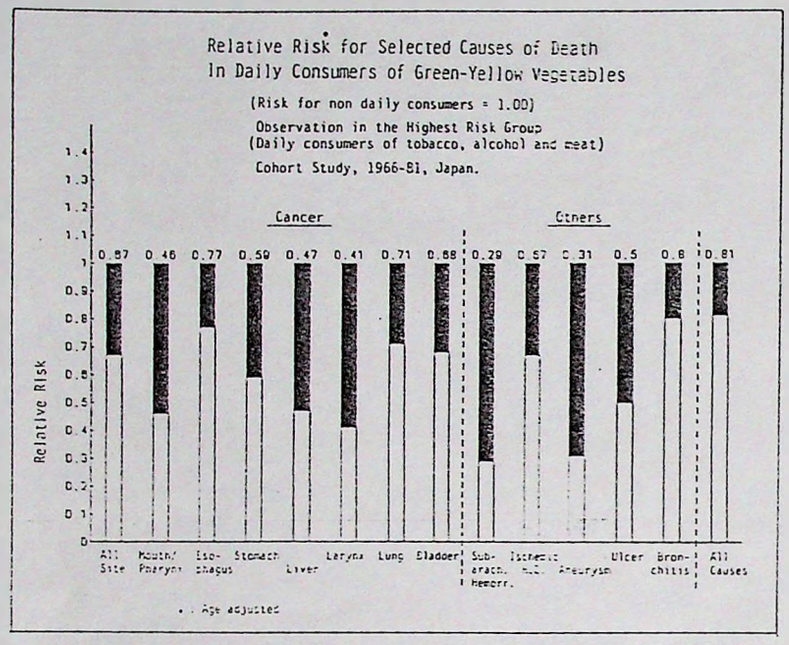

FIG. 1

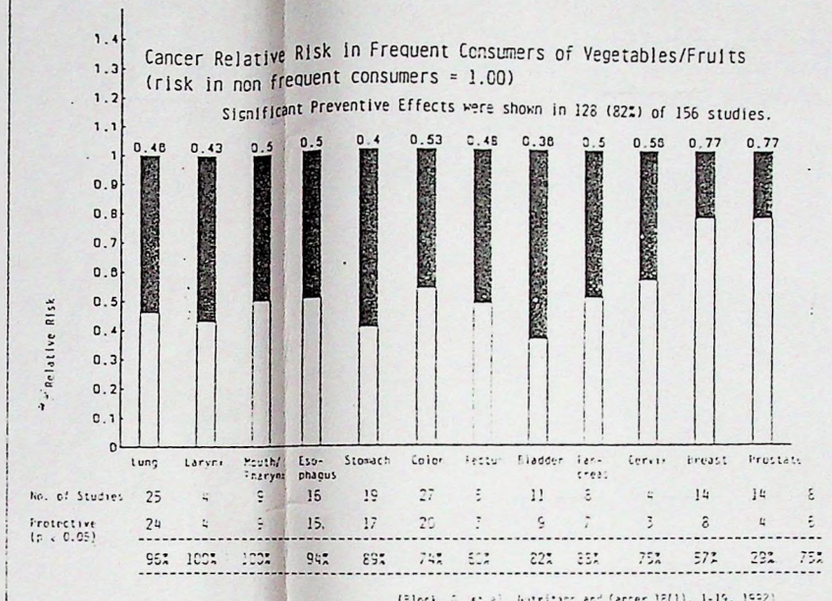

FIG. 2

Thus risks for cancer of many sites in those consuming GYV frequently and in particular with higher serum level of beta-carotene have been shown by many cohort studies to be one half or even one fifth compared with lower serum level individuals.

A cohort study is in progress in Yakumo town in Hokkaido in which serum level of beta-carotene was measured for 2,356 inhabitants and these subjects are under follow-up according to the initial serum level of beta-carotene. After 5 years, multifactor adjusted cancer mortality ratio for individuals with low, medium and high titer of serum beta-carotene was 1.00, 0.41 and 0.21 (Sasaki et al, 1992)(9). In other words, cancer risk is about one fifth in subjects with high beta-carotene titer (31.9μg /dl-) compared with low titer subjects (-14.2μg/dl).

Intensive public education should therefore be focussed on cessation of tobacco use and on daily consumption of GYV with slogans such as 'carotene instead of nicotine', 'prevent cancer by one carrot a day'. Public education should be easy to understand, and easy to practice. Message based on convincing scientific evidence should be given with confidence in most persuasive way. Above shown slogans are made for such purpose and have been proved to be quite effective in changing public behavior (10) e.g. GYV per capita consumption doubled since 1960 in Japan.

Increased consumption of vegetables in general and fruits are also recommended. Out of 156 epidemiological studies conducted to examine effect of increased consumption of vegetables and fruits on the risk of cancer of many sites, 128 (82%) showed significantly lowered risk in frequent consumers as shown in Fig. 2 (modified from the report of Block et al, 1992)(11).

RISK FACTORS AND PROGNOSTIC FACTORS

As a by-product of our large scale cohort study in Japan it was revealed that selected risk factors which govern onset of cancer also operate to modify prognosis of cancer as well (12).

Daily smokers of cigarettes showed significantly worse prognosis of lung cancer than nonsmokers, risk of dying (age, sex, other life-style adjusted) within one year after diasnosis being 1.89 (1.37-2.60). Daily alcohol drinkers exhibited significantly worse prognosis of esophageal cancer than non daily drinkers, risk of dying within one year after diagnosis being 1.82 (1.21-2.75). Daily meat consumers showed significantly worse prognosis of breast cancer than non daily consumers, risk of dying within 6 months after diagnosis being 5.86 (2.35-14.61).

Thus if we are successfully control such life-style risk factors we can expect far better clinical course than otherwise even in case the disease does occur. This particular point must also be a blessing news to the people in developing countries.

VACCINATION

Vaccination has also potentials for primary prevention since selected chronic virus infections have been shown to promote risks for cancer of liver (hepatitis B and C virus), cervix (human papilloma virus), nasopharynx and Burkitts tumor (EB

virus), Kaposi sarcoma (HIV) etc. Among these, vaccination programmes against Hepatitis B virus infection have already been started by the initiative of WHO (IARC) in selected countries in Africa and Asia (1).

Until vaccination programmes for other cancers become also available, above stated life style modification must be the most effective strategies for cancer prevention and control in developing countries.

CONCLUSIONS

Innovative weapons to prevent and even to eradicate cancer might become available sometimes in the next century using rapidly developing molecular biology. However, at least in our generation, cancer prevention must rely heavily on conventional weapon called life-style modification especially in developing countries, where effectiveness of such methods is believed to be high and, above all, practical. Put them into practice now. Try to prevent millions of people in developing countries from becoming cancer victims making full use of conventional but still surprisingly effective weapons named life-style modification with slogan such as 'Carotene instead of Nicotine'.

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1

EPIDEMIOLOGICAL OBSERVATIONS OF HEAD AND NECK CANCER

D. N. Rao[1] and B. Ganesh[2]

In this chapter, the main emphasis is to bring out the salient epidemiological observations on head and neck cancer in the Indian subcontinent. In addition, efforts are also made to bring out the changes in site-specific incidence rates and identify high risk groups in head and neck cancer. Associated dietary factors, occupational hazards and experimental evidences are also discussed in detail.

Based on the International Classification of Disease (ICD 9th Revision)[1] the sites in the oral cavity (ICD:140-145), pharynx (ICD:146-148), larynx (ICD:161) and paranasal sinus (ICD:160) together constitute the head and neck region. The oral cavity includes the upper and lower lip, anterior two thirds of the tongue, salivary glands, gum (upper and lower), floor of the mouth, buccal mucosa including the trigone region and the hard palate. Paymaster (1965)[2] reported that cancer in the base of the tongue should be separated from that of the oral tongue and be considered as part of the oropharynx along with the soft palate and tonsil. The current international coding system has yet to recognise this fact and the site continues to be included in the oral cavity.

Descriptive epidemiology

1. Historical Review

Cancer as a disease is well known in India since vedic times. Scripts written in Devanagri dialect give a fair description of the disease entity, its surgical management and transplant techniques.[3] Even in the beginning of this century, the problem of cancer in India and the need to have data was voiced in the House of Commons in London.[4] A survey of 15 missionary and 34 Government hospitals in Travancore indicated that oral cancer accounted for 38% of all cancers.[5] From a study of autopsy data and pathology records covering many centres all over India, Vishwanath and Grewal reported that a high frequency of buccal cancer was seen in the Indian population.[6,7,8]

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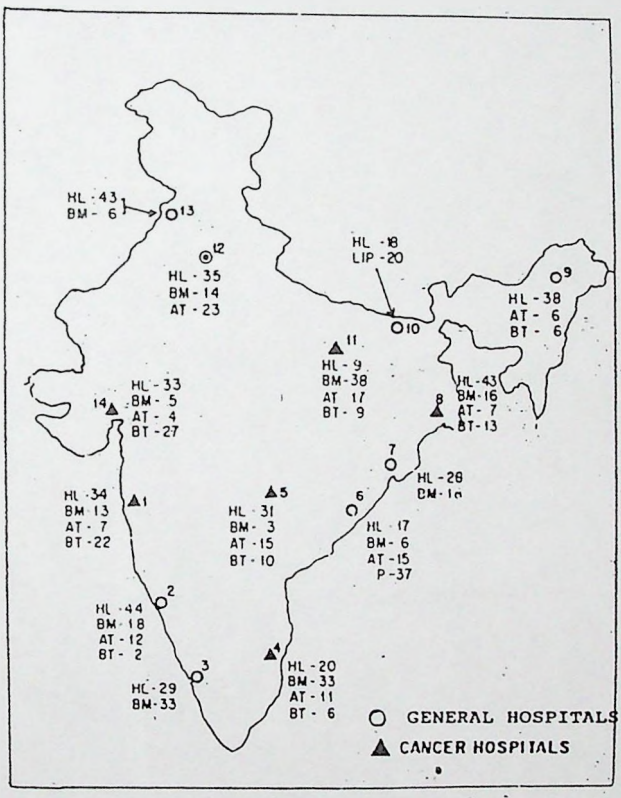
The cancer pattern in the Indian subcontinent until the 1960s was evaluated mainly by the use of hospital records and pathological reports. Head and neck cancer accounted for about 50% of all cancer at the Tata Memorial Hospital (TMH).[2] Similar observations were also present in the data obtained from general and cancer hospitals in the country. During the 1970s, cancer statistics from general and teaching hospitals in India[9] showed striking variations in the relative frequency of certain anatomical sites in the head and neck (Fig.1).



HL - Hypopharynx and Larynx
BM - Buccal Mucosa
AT - Anterior Tongue
BT - Base Tongue
P - Palate

Fig. 1. Relative frequency of head and neck cancer in cancer and general hospitals in India.

Data from South India (Cancer Institute, Madras and Kasturba Medical Hospital, Manipal), showed a higher percentage of buccal cancer and anterior tongue cancer. Base tongue cancer was common in Western India (TMH, Bombay (22%) and in Gujarat Cancer Hospital, Gujarat (27%)), compared with other hospitals in the country. This survey also brought out certain observations such as the high percentage of lip cancer (20%) in Bihar in Northern India, hard palate cancer (37%) from the coastal districts of Andhra Pradesh in Eastern India and hypopharyngeal cancer (38%) in Assam in the North East of the country.

Nasopharyngeal cancer is rare in the Indian population. Paymaster (1965)[2] indicated that, unlike other cancers in the head and neck, nasopharyngeal cancer showed a double peak in the age pyramid (Fig.2 :: one in the age group 15-24 years, and the other in the age group 45-54 years. Interestingly an analysis of 560 histologically confirmed cases showed that, in both sexes, only the poorly differentiated type showed the younger age peak, while in well differentiated squamous carcinoma the peak appeared in the older age group.[10,11]

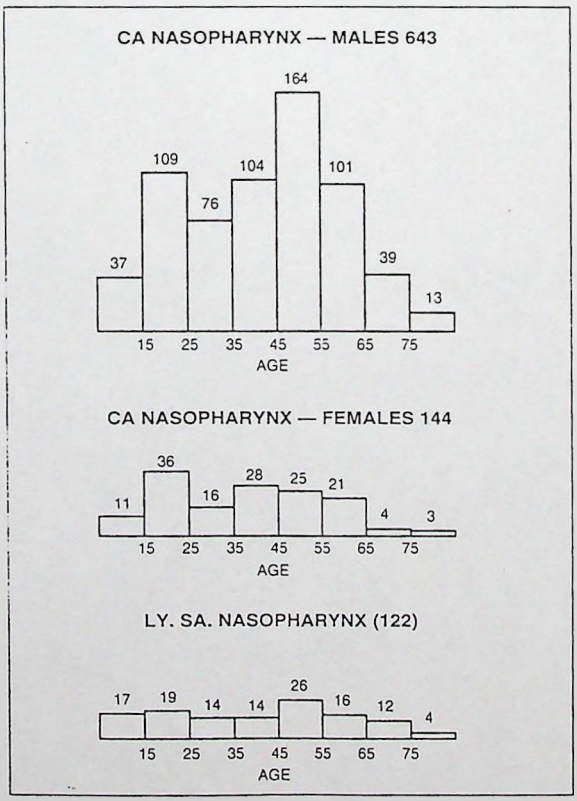


Fig. 2. Carcinoma of the nasopharynx. Tata Memorial Hospital (1941-1974).

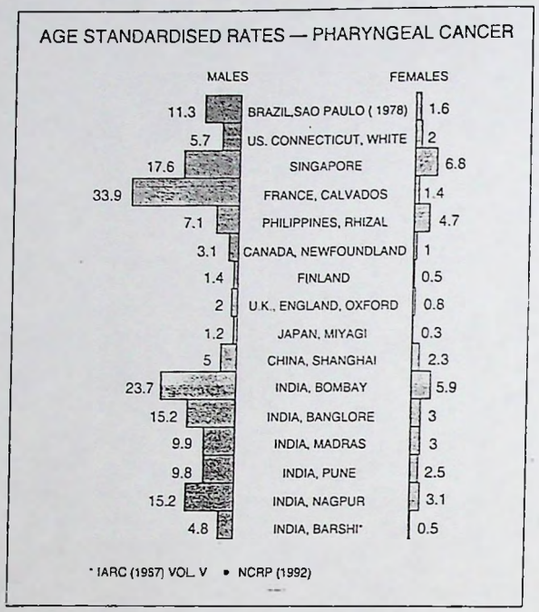


Fig. 3. Age standardised rates for pharyngeal cancer.

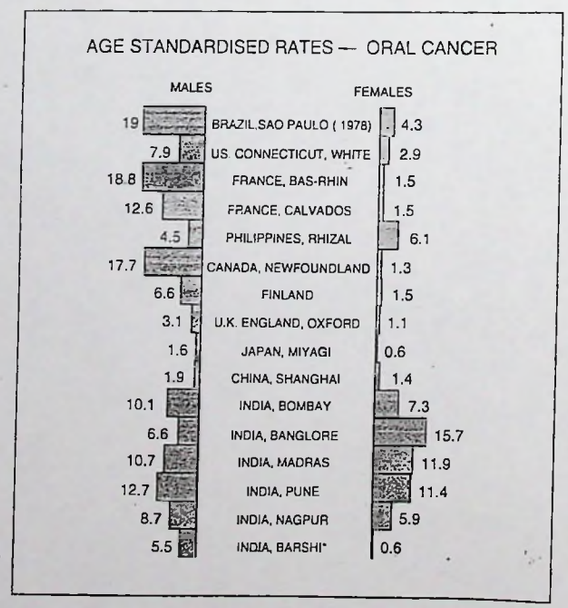


Fig. 4. Age standardised rates for oral cancer.

Incidence — The Indian scene

The computed age-standardised rates for three major groups in head and neck cancer; oral cavity (ICD:140-145), pharynx (ICD:146-149) and larynx (ICD:161), in metropolitan registries in India along with the rates in selected countries/populations are shown in Figs. 3, 4 and 5 respectively. The age standardised incidence rates for oral, pharyngeal and laryngeal cancers are high in both males and females in all metropolitan registries in India.[12]

The only rural cancer registry in India is in Barshi, a town in Sholapur District of the State of Maharashtra. The rural registry covers 134 villages with a population of 1,85,296 people. The age-adjusted incidence rates in males and females were 57.6 and 52.2 per 100,000 for all sites respectively and these rates were lower than the rates in urban registries. Since 80% of the Indian population lives in rural areas, the rates in Barshi may have to be considered in assessing the true picture of cancer in India.[13]

Age-standardised rates according to fourth digit of ICD-9 for oral, pharyngeal and laryngeal cancer seen in six metropolitan registries in India for males and females are shown in Table 1. In general, the oral tongue, alveolus and mouth are the major sites affected in the oral cavity. The

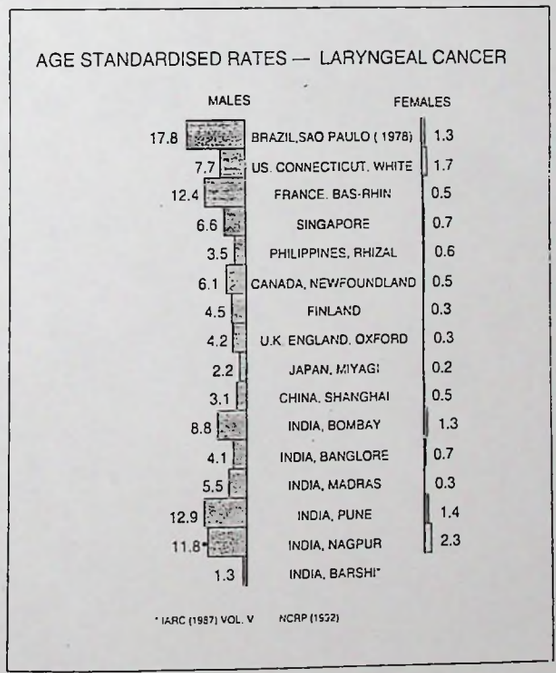


Fig. 5. Age standardised rates for laryngeal cancer.

hypopharynx is a major site for pharyngeal cancer in both males and females respectively. The rates for males are higher compared to females at all sites in the head and neck except in the Bangalore registry where the rates for buccal mucosa cancer in females are higher than those in males. In particular, high rates in males are observed in Madras for mouth cancer, in Bombay, Nagpur and Poona for cancer of the anterior two thirds of the tongue, and in Bombay and Ahmedabad for cancer of hypopharynx and base of the tongue.

Nasopharyngeal cancer is a rare disease among caucasians but is one of the more common tumours occurring in individuals in the south-eastern region of China, among migrants from that geographical area and their descendants. The highest incidence reported is from Hong Kong where the annual incidence of nasopharyngeal cancer is 30 and 12.9 per 100,000 among males and females respectively. In India the age-standardised rates range from 0.23 in Ahmedabad to 0.9 in Bangalore for males whereas for females the rates vary from 0.08 per 100,000 in Ahmedabad to 0.3 per 100,000 in Bombay, Nagpur and Madras. Data from the TMH cancer registry shows that although this cancer forms less than 1% of all cancers, the distribution according to place of residence indicates that the frequency of nasopharyngeal cancer is high in patients from the North Eastern region (Table 2). As there is no population based registry in that region, the high incidence of this cancer is not yet confirmed.

Incidence – Worldwide

Lip cancer is uncommon in males and very rare in females. Cancer of the lip is very rare in Asia. Incidence is high in South Australia and New Foundland (Canada). The incidence is low among U. S. blacks. Generally, the incidence of lip cancer is decreasing worldwide.

Tongue cancer incidence is high among Indians and also among males in France and Switzerland. The sex ratio is of the order of 3 in India, 8 in Geneva (Switzerland) and 13 in Bas-Rhin (France). The risk of cancer of the tongue among males is reported to be increasing in several populations in the U.S.A.

The incidence rate of cancer of the mouth (gum, floor of mouth, mucosa of the cheek, hard and soft parts of the palate and uvula) has more than doubled in a short period of 15 years in Miyagi and Osaka prefectures in Japan.[14]

The incidence rate and number of new cases of 18 different cancers have been estimated for the year 1985 in 24 areas of the world.[15] About 7.6 million (excluding non melanoma skin cancer) persons in the world developed cancer. The majority of them, about 52%, were estimated to be in the developing countries. Cancer of the mouth and pharynx was third in order among males (about 1,87,000 new cases) and fourth in order among females (about 1,14,000 new cases) in the developing countries. Among 8,06,900 estimated total cancer cases in Southern Asia (India, Pakistan, Iran and Bangladesh) in 1985, cancer of mouth and pharynx accounted for 1,42,900 persons (17.7%) and laryngeal cancer 31,200 (3.9%).

Table 1

Age Standardised Incidence Rates per 10^5 for head and neck cancers in major metropolitan cities in India*

Males

Site	(ICD-9)	Bombay	Bangalore	Madras	Ahmedabad#	Nagpur	Poona
Oral Cavity	(140-145)						
Lip	(140)	0.3	0.3	0.3	0.16	0.3	0.9
Tongue	(141.1-9)	3.3	1.8	2.3	10.56+	3.2	3.5
Gum	(143)	1.8	1.0	0.6	0.87	2.2	3.2
Floor Mouth	(144)	0.7	0.7	0.3	0.61	0.3	0.1
Other Mouth	(145.0-1.6)	2.7	1.9	5.5	3.98++	1.8	3.7
Pharynx							
Base Tongue	(1410)	6.1	3.2	2.0	+	5.1	1.4
Palate	(145.3-5)	1.2	0.6	1.4	++	0.7	0.9
Oropharynx	(146)	3.5	2.4	2.4	3.89	4.5	2.0
Nasopharynx	(147)	0.8	0.9	0.7	0.23	0.3	0.6
Hypopharynx	(148)	9.9	5.4	4.2	8.54	6.5	4.7
Pharynx NOS	(149)	3.4	0.4	0.6	1.61	1.1	1.1
Larynx	(161)	10.0	5.0	5.3	7.01	11.8	12.9
All Sites	(140-208)	145.0	103.2	92.1	110.19	122.5	134.1

Females

Site	(ICD-9)	Bombay	Bangalore	Madras	Ahmedabad	Nagpur	Poona
Oral Cavity	(140-145)						
Lip	(140)	0.2	0.1	0.3	0.15	0.2	0.5
Tongue	(141.1-9)	2.1	0.5	1.6	2.1+	1.1	–
Gum	(143)	1.2	2.8	1.4	0.71	1.9	1.9
Floor Mouth	(144)	0.2	0.4	0.1	0.03	0.1	0.1
Other Mouth	(145.0-1.6)	2.9	10.9	7.9	1.65++	1.8	–
Pharynx							
Base Tongue	(1410)	1.3	0.7	0.5	+	1.0	–
Palate	(145.3-5)	0.5	0.3	0.7	++	0.2	–
Oropharynx	(146)	0.8	0.5	0.9	0.42	0.7	0.4
Nasopharynx	(147)	0.3	0.1	0.3	0.08	0.3	0.2
Hypopharynx	(148)	2.2	1.4	1.2	2.04	1.0	1.5
Pharynx NOS	(149)	1.3	0.3	0.1	0.23	0.1	0.4
Larynx	(161)	2.0	1.5	0.7	0.51	2.3	1.4
All Sites	(140-208)	126.0	139.7	120.6	81.79	108.7	146.2

* *IARC (1987)*[12]
\# *Patel et al. (1991)*[76]
\+ *includes Ant. tongue*
++ *includes Other mouth*

In Southern Asia, over 5,76,200 persons were estimated to have died due to cancer in 1985. Among all cancers 65,300 males and 40,400 females were estimated to have died due to cancer of the mouth and pharynx. The high incidence and mortality rate due to this cancer in this region have been attributed to tobacco chewing and smoking.[16]

EDITORIAL

CHALLENGES AND REALITIES FOR THE COMING DECADES

Dr. P. B. Desai*

Introduction — Epidemiology and prevention — Prophylaxis and early diagnosis — Fundamental and applied research in head and neck cancer — The concept of organ preservation in head and neck cancer — Combined treatment modalities — Predicting treatment responses (predictive oncology) — Rehabilitation and terminal care — Where do we go from here?

Introduction: Despite our current technical capabilities in research and treatment methodologies, cancer of the head and neck continues to present major challenges to all the major oncologic disciplines worldwide. As we approach the turn of the century, the morbidity and mortality due to this highly preventable cancer has not shown a downward trend: this, despite head and neck cancer being a classic module for research, prevention, prediction and effective treatment. Collated efforts towards the control and cure of head and neck cancer worldwide and especially in the region where it is a common disease are not only worthwhile but need to be intensified in a pragmatic manner. There is now enough and more knowledge about the disease not only to prevent but to predict, to ensure prophylaxis, to diagnose early and treat effectively often ensuring organ and function preservation. This knowledge has accrued by the combined efforts of many workers in different oncology disciplines dealing with head and neck cancers. We now have to develop an effective methodology, within institutes and beyond to enable us to reach out to the community for the control and cure of head and neck cancer.

Epidemiology and Prevention: Exhaustive reviews and studies appear in this volume with special reference to South Asia where head and neck cancer forms nearly 27% of total cancers.[1] This contrasts with about 5% incidence in the western world. That tobacco usage in different forms is a major contributing cause is a well established fact and no further debate need be encouraged on this issue. Tobacco usage in South Asia differs greatly from the usual smoking habit in the west. Chewing tobacco with multiple other ingredients (betel nut, betel leaf, lime, catechu, etc.) is a major cause of buccal mucosa and gingival cancers. The quid bolus with

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tobacco leaves is kept for hours on end in the buccal mucosa or the gingivo-buccal sulcus and a cancer developing on the exact site has a direct cause and effect relationship. The left buccal mucosa will be spared if the bolus is kept on the right side (and vice versa), and for good reasons it is referred to as the Indian buccal mucosa cancer where the habit of tobacco chewing is most prevalent. The rare habit of reverse smoking in South India, with the lighted end in the mouth produces cancer of the soft and hard palate which is the target point of inhaled tobacco smoke.

Tobacco induced premalignant lesions like erythroplakia and certain forms of leukoplakia are now well documented and clearly the case for primary and secondary prevention of oral cancers cannot be disputed. Field surveys have shown that certain forms of leukoplakia and erythroplakia are reversible[2] upon cessation of the tobacco habit; hardly 5 to 8% of leukoplakias have a malignant potential and these must be prophylactically excised to ensure cancer prevention. Secondary prevention in high risk individuals with tobacco usage merits a yearly clinical examination and cytology studies as needed. Excision of suspect lesions of nodular forms of leukoplakia will contribute significantly to a reduction in oral cancer incidence, though no hard data are yet at hand. All medical expertise may not be available in rural societies and these approaches could also be implemented by well trained health care workers particularly in developing areas of the world. Education at all levels — the public, the youngster at school, the health worker or the paramedic and the family doctor, is crucial and should be the central point of reference in the control of head and neck cancer. Despite all our knowledge, prevention of cancer in general, and head and neck cancer in particular is neither cheap nor cost effective and is not always easy to justify. Educating the public, surveying the population, training the paramedic or the doctor, studying premalignant lesions by cytology or excision biopsy and its interpretation, modifying habits and life styles, may be much more costly than therapy itself. Research in preventive oncology and its effective implementation has been successful in very few instances (lowering of tobacco usage in the USA, cervical cancer reduction or downstaging in selected western societies) at a cost which most nations will find difficult to bear and sustain. Nonetheless, to implement prevention wisely and pragmatically with a positive cost benefit outcome will require the skill and enthusiasm of many different experts. That it can be done is beyond doubt, witness to which is the downstaging data on cervical and oral cancers now available from the rural cancer registry of the "Barsi" area, an effort 12 years in the making by the Tata Memorial Centre in its rural satellite centre.[3]

Prophylaxis and early diagnosis: Prophylaxis has been alluded to earlier on and it would suffice merely to state that the premalignant lesions in the head and neck region, particularly the

oral cavity (which form 33% of all cancers of the head and neck)[4] are so well defined that efficient cancer prophylaxis can be ensured in high risk groups at least for oral cancers. The oral cavity, the oro and hypopharyngeal regions are the most easily accessible sites for visual examination. Efficient endoscopic survey of the upper aerodigestive tract cannot possibly miss an early T1 lesion in these anatomic sites. Field surveys in high risk endemic areas, undertaken by medical personnel and well trained health workers[5] have shown conclusive evidence of not only being able to downstage the disease but also to ensure good cancer prophylaxis either by simple excisional surgery of premalignant lesions and/or reversal of abnormal mucosal changes to normalcy by reverting back to more prudent habits and lifestyles.[5]

Combined treatment modalities — The concept of organ preservation in head and neck cancer: The conceptual changes now being witnessed in cancer therapy in general and head and neck cancer in particular are based mainly on the understanding of the strengths and weaknesses of each of the major therapeutic disciplines viz. surgery, radiotherapy and chemotherapy. Local failures are the main causes of morbidity and mortality in head and neck cancer though an increasing frequency of distant metastasis in long term survivors are now well documented.[6] Increasing sophistication in radiotherapy techniques including brachytherapy and more efficient cytotoxic drugs and their appropriate combination have produced more efficient local control in head and neck cancers, thus helping to avoid the morbidity associated with the removal of the larynx, pharynx and a total glossectomy. Current literature is replete with such reports of organ preservation in head and neck cancers with chemo-radiotherapy.[7-9]

What will be crucial to this effort is to predict chemo-radiosensitivity or resistance of a given cancer "ab initio" so that the appropriate initial therapy is instituted to the best advantage of the patient. It is prudent to keep in mind that salvage surgery after failed chemo-radiotherapy has a better chance of success than the control of a post surgical recurrent cancer by chemo-radiotherapy salvage. Important studies regarding the ability to predict tumour radio-chemosensitivity/resistance are on and an appropriate decision in this regard will increase the chances of a prolonged control/cure and significantly decrease the morbidity and mortality associated with improper or inadequate initial therapy. The concept of combined treatment modalities in head and neck cancer is now well entrenched and a surgeon, radiotherapist or chemotherapist treating head and neck cancers in isolation renders great disservice to an afflicted patient. This parallels the successes achieved in conservation of the organ and function in breast cancer and in bone and soft tissue malignancies.

Fundamental and applied research in head and neck cancer: As the clinical sciences of the 1950s and 1960s move towards the increasing technologic and biologic sciences of the 1980s

and 1990s, our conceptual understanding of the anatomico-pathologic basis of cancer and its therapy is undergoing a gradual change. This is just as it should be, for, in-vitro studies of tumour biology in the laboratory may not identically reflect all the nuances of in-vivo interactions between the tumour and the host. Conventional treatment methods evolved after many years of knowledge based on clinical experiences and anatomico-pathologic studies cannot be quickly or suddenly modified or jettisoned at the altar of the emerging new biology; admittedly, the new science is providing us with a deeper insight into predictive oncology — predicting treatment responses, more effective prognostication and even in some situations helping us to identify a very high risk individual among a group of healthy individuals predisposed to malignancy because of their habits and lifestyles.

Head and neck cancer provides an ideal module to study a cancer site in its totality; from fundamental research and its impact on diagnosis and treatment, its preventive potential and also effective steps to be taken for rehabilitation and terminal care. The chapters in this volume address all these issues including the emerging biology of head and neck cancer, viz. tumour ploidy, oncogene and cytokeratin expression in the tumour cells, growth factors and their corelation with the clinical state of the disease and its behaviour and prognosis.[5-10] Lessons have to be learnt, slowly and carefully, so that the knowledge and understanding of tumour biology can be dovetailed into clinical oncology.

Predicting treatment responses: Predictive oncology is an emerging science based on our past knowledge and current understanding of tumour biology. The morphologic characteristics of the tumour whether proliferative and non-infiltrating or infiltrating and submucosally spreading, often determines treatment responses. The majority of the former tumour types will respond, often dramatically to radiotherapy and chemotherapy, whereas the infiltrating, submucosal spreading type of cancers do poorly with chemo / radiotherapy. Initial surgical removal in the latter group will save much morbidity of unnecessary chemo-radiotherapy. In contradistinction, surgical ablation and its attendant morbidity of organ losses could be avoided in the proliferative, non-infiltrating type of tumours. This prediction will have a concordance in nearly 80% of cancers and a multivariate analysis of other biologic factors, "*beyond morphology*", those of tumour ploidy, cytokeratin and oncogene expression, S-phase growth factors may help us to predict the tumour behaviour vis-a-vis tumour response and prognostication in the other 20% of patients.[11] The human system is not a mathematical model and constant endeavours will be needed at all times to collate all the factors before treatment decisions can be made.

It is an accepted fact that the majority of T1 & T2 lesions can be effectively treated with either surgery or radiotherapy singly or in combination, whereas treatment response predictions

will be of greater value in the locally advanced cancers to avoid treatment related morbidity. Overall results are similar and morbidity often lesser with chemo-radiotherapy in selected T3 – T4 lesions thus allowing us to preserve organal function so vital in the head and neck region.

Predictive oncology goes beyond the realms of treatment response, prediction and prognosis. In the years to come it aims to explore and decipher the very basis of genetic predisposition by studying the chromosomal aberrations either endowed or acquired by insults of habits, life styles or other carcinogenic factors. The implications for prophylaxis, early diagnosis and effective treatment appear exciting; to translate it into clinical realities and application will require an enormous amount of infrastructure, not entirely easy to create. The present era of excitement generated by increasing understanding of tumour biology needs to be tempered by cautious and sober optimism.

Rehabilitation and terminal care — Where do we go from here? Despite our present capabilities in research, prevention, early diagnosis and effective treatment of head and neck cancers, at least 50% of patients currently undergoing treatment will require appropriate post therapy rehabilitation care and many of them will need good terminal care and pain relief. In the excitement and glamour of research and therapy, these areas are often neglected and only the most human amongst the medical and paramedical groups will be able to provide this care. Whether it is a hospice facility or home care, nursing or availability of simple pain relief medications (oral morphine or injectible analgesics), human interactions in terminal stages of uncontrolled cancer is crucial for a holistic care of the cancer patient. Stressing this need may appear simplistic but without doubt this is a most glaring lacuna globally and more so in developing countries in our overall cancer effort worldwide.

In an era of continuing resource restraints, creation of large comprehensive cancer centers is not only prohibitively expensive but probably even unnecessary. There is indeed much medical capability beyond the formal institutions and these should be harnessed to create smaller, more functional centres where reasonably adequate facilities for field work, prevention, education, statistical collation, early diagnosis and effective treatment by surgery, radiotherapy and chemotherapy could be organised. Such *"community cancer centres"*,[12] within reasonable budgetary possibilities are not difficult to envisage or create. This will lead to an equitable distribution of cancer health care not only in the developing areas of the world but even in the advanced countries where such lacunae still exist. If our experience at the rural satellite centre at Barsi is any indication, the future of a patient with head and neck cancer, or for that matter any cancer will be more secure by adopting a pragmatic approach which can encompass a holistic attitude towards a patient afflicted with cancer.

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Trends

It is well known that changes in life style in terms of the tobacco habit and alcohol usage, and also withdrawal or introduction of a carcinogen in the environment are likely to affect the trend in the incidence rate of cancer. Long periods of observation are necessary to assess the increase or decrease in the incidence rate.

According to a recent IARC report,[14] global trends in cancer incidence and mortality show variations at most sites. In particular, for head and neck cancer, lip cancer is declining in most parts of the world and tongue cancer which is common in India, France and Switzerland, also shows a declining trend.

There has been a dramatic decrease (40%) in the frequency of head and neck cancer over the years at TMH. The decrease was observed in all the major sites of head and neck cancer except that there was a slight increase in the percentage of nasopharyngeal cancer.

In order to confirm this, incidence data from Bombay Cancer Registry was used to analyse the trend in head and neck cancer. The site specific age adjusted incidence rates for major sites in head and neck cancer in males in Bombay between 1964 and 1982 are shown in Table 3. The incidence rate of cancer of the tongue declined gradually from 14.0 per 100,000 in the earlier period (1960s) to 9.7 per 100,000 in 1978-82, while cancers of 'other parts of the mouth' remained more or less stable over the years with an age-adjusted rate of about 7.0 per 100,000. The rates for oropharyngeal cancer declined from 6.1 per 100,000 to 3.5 per 100,000 over the years; whereas the incidence of hypopharyngeal cancers increased from 7.3 to 10.0 per 100,000. There was a declining trend for laryngeal cancer in Bombay.

The average percentage change in incidence rate for cancer of the tongue, oropharynx and larynx, showed a statistically declining trend.[15] Further analysis of cumulative incidence rates for these sites in Bombay males showed that the decline in the trend was due to a cohort effect. The observed changes in incidence rates probably reflect the changes in tobacco usage over the years i.e. a marked decrease in bidi smoking, a known high risk factor for these sites.

Influence of religious and endogamous groups

Epidemiological studies carried out in various parts of the world have shown that the cancer patterns change according to life styles apart from environmental and other factors. Age-standardised incidence rates by religion and sex for sites in head and neck cancer for Greater Bombay population are presented in Table 4. High incidence rates of tongue, mouth and hypopharyngeal cancers were observed in all the religious groups. Parsis, followers of the Zorastrian faith, mainly live in Bombay and by religious customs, tobacco chewing and smoking are strictly

Table 2
Regional variation in the relative frequency of nasopharyngeal cancer in India

	Number of patients		Rel. Frequency %
	All Cancer	Nasopharyngeal Cancer	
All India	118199	785	0.66
Cancer Hospitals			
Calcutta	6326	42	0.66
Hyderabad	11711	86	0.73
Madras	5520	38	0.69
Bombay	24178	171	0.71
Ahmedabad	8139	44	0.54
Kanpur	8457	40	0.47
General Hospitals			
North-East India	2608	42	1.61
Assam (1)	5195	63	1.21
Bengal & North Bihar (2)	13214	104	0.79
South-East India (5)	8811	31	0.35
South-West India (8)	10199	45	0.44
West India (9)	4231	29	0.69
North-West India (3)	9610	50	0.52
North India (5)			

Figures in parentheses indicate the number of hospitals from that region
Source: Jussawalla D J and Gangadharan P[9]

Table 3
Site-specific age adjusted rates for cancers in males in Bombay 1964-82

Site of malignant neoplasm	Age adjusted incidence rate (world) per 100,000			
	1964-66	1968-72	1973-77	1978-82
Oral cavity	14.0	12.6	10.2	9.7
Tongue	7.0	7.3	6.7	7.5
Mouth (all other parts)				
Pharynx	6.1 *	5.6	4.5	3.5
Oropharynx	7.3	7.7	8.7	10.0
Hypopharynx	13.8	13.6	12.4	10.1
Larynx	139.5	143.1	142.1	147.4
All Sites				

* *ICD 7,145: tonsils and oral nasopharynx*
Source: Reference Nos. 10, 19, 81, 84

prohibited. This community belongs generally, to a higher income group and follows a westernised life style. The Parsi community also has a higher percentage of persons in the older age group compared to the total Bombay population.[18] Among Parsis in both sexes, high incidence of laryngeal cancer is observed as compared to other communities even though tobacco habits are forbidden in that community. The rates for Indian Christians are found to be higher for tongue, oropharynx and hypopharyngeal cancers. The reason for this is not known and it may be due to a more westernised life style, with a higher percentage of cigarette smokers and alcohol addicts in this community.

Table 4

Age adjusted incidence rates (per 10^5) by religion and sex, Greater Bombay, 1979-84

ICD	Site	Hindus		Muslims		Christians		Parsis	
		Male	Female	Male	Female	Male	Female	Male	Female
140	Lip	0.2	0.1	0.2	0.1	0.2	–	0.7	0.6
141	Tongue	4.3	1.5	4.9	1.6	7.0	1.9	4.6	6.3
143	Gum	0.7	0.7	0.7	0.6	0.9	0.2	2.0	1.3
144	Floor Mouth	0.3	0.1	0.3	0.1	1.2	0.3	–	–
145	Other Mouth	2.4	2.0	2.7	1.8	2.5	1.3	2.6	2.5
146	Oropharynx	1.7	0.4	2.2	0.3	3.2	0.5	0.7	0.6
147	Nasopharynx	0.5	0.2	0.5	0.3	1.0	0.2	1.3	–
148	Hypopharynx	4.6	1.3	5.6	1.1	6.3	0.9	2.0	0.6
149	Pharynx NOS	1.1	0.4	1.3	0.5	2.1	0.5	0.7	1.3
161	Larynx	4.1	0.8	5.0	1.2	5.6	0.7	10.6	3.2

Source: Reference Nos. 77, 78, 79, 80.

A study on the distribution of cancer in some endogamous groups using TMH hospital data (1946-50) showed variations in the site distribution of cancer among Hindus from Maharashtra. The sub-castes considered were marathas (40% of Hindus), occupational castes, brahmins and harijans. Oral and pharyngeal cancers accounted for 50% of all male cancer cases in brahmins, whereas in other sub-castes the percentages were 67% in harijans, 64% in marathas and 64% in occupational castes. This pattern was also seen in females. Oral cancer, in particular, was less predominant among brahmins (12%) as compared to other sub-caste groups (20-33%). The study showed that the observed variation in the relative frequency of oral cancer in Hindu sub-castes could be due to variation in tobacco habits.[19]

Migrant Studies

Epidemiological studies on migrant populations have shown change in the site-specific incidence rates and the pattern of cancer compared to the host population. Indians from southern parts of India, mainly Tamil speaking people from the state of Tamil Nadu, migrated to Singapore and Malaysia whereas persons from the western part of India, Gujarathi speaking Indians migrated to South Africa (S.A.). The incidence rates for head and neck cancer among migrant Indians are shown in Table 5. Migrant Indians generally follow the same life style and continue their chewing and smoking habits. Because of continuing habits, the incidence rates among migrant Indians are comparatively higher for some of the sites in head and neck cancer than the native population. Migrant Indian females have high rates for cancer of the mouth and pharynx compared to the corresponding rates in native African females in Natal (S.A.).

Table 5

Age standardised rates for head and neck cancer among migrant Indians (Natal, South Africa and Singapore)

Site	Madras * Indians (1982)		Singapore * Indians (1978-82)		Bombay @ (1964-66)		Natal @ Africans (1964-66)		Natal @ Indians (1964-66)	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Lip	0.3	0.3	0.3	–	0.4	0.4	0.4	0.3	0.8	–
Tongue	4.3	2.1	4.6	3.3	14.0	3.7	1.8	0.7	1.5	3.0
Sal. Gland	0.3	0.2	0.5	1.2	0.1	0.2	0.8	0.8	0.7	0.4
Mouth	8.1	10.0	4.4	9.6	6.5	5.9	3.7	0.5	4.4	8.1
Oropharynx	2.4	0.7	3.7	3.1	#	#	#	#	#	#
Nasopharynx	0.7	0.3	0.3	1.3	0.6	0.5	0.0	0.2	–	–
Hypopharynx	4.2	1.2	3.6	1.6	#	#	#	#	#	#
Pharynx	0.6	0.1	1.0	1.0	#	#	#	#	#	#
Larynx	5.3	0.7	8.2	1.6	13.8	2.8	4.5	0.5	3.5	–
Other Pharynx	–	–	–	–	16.0	4.4	4.0	0.5	1.0	2.1

* *IARC (1987) ICD-9th Revision*
@ *UICC (1970) ICD-7th Revision*
\# *included in other pharynx*

Multiple Primaries

The appearance of a second cancer among head and neck cancer patients has been reported in the literature. Based on the TMH data, Vyas et al[20] have reported the occurrence of multiple primaries in an Indian population (Table 6). The study pointed out that patients with a primary cancer in head and neck region did not discontinue their tobacco habits. This resulted in the appearance of a second cancer at susceptible sites such as the lung, other head and neck sites and the oesophagus.

Table 6
Multiple Primaries in Head and Neck Cancer
Tata Memorial Hospital 1941 - 85

Site	First Primary	Site	Second Primary
Laryngeal apparatus	31	Lung	29
Anterior tongue	9	Esophagus	12
Base tongue	8	Head and Neck	19
Buccal Mucosa	8	Others	11
Oropharynx	4		
Postcricoid	2		
Lower alveolus	2		
Nose	2		
Nasopharynx	1		
Tonsil	1		
Soft palate	1		
Thyroid	1		
Upper alveolus	1		
	71		71

Source: Vyas et al (1983)[20]

Analytical studies

In the following discussion, each of the known risk factors are summarized along with the risk estimates (Table 7). The factors considered are betel quid chewing, smoking, snuff dipping, use of masheri and nass/naswar, alcohol consumption, diet and occupational exposure.

Tobacco

Tobacco in India, is used in various forms. Placement of quid in the buccal cavity is quite common. The various forms of chewing are pan (betel leaf), betel-nut, pan with chewed fine tobacco, pan with lime and tobacco. The types of chewing habit vary across the country.

Local customs and habits play an important role in the high incidence of oral and pharyngeal cancer in India. Since ancient times pan with betel nut are offered during religious functions and celebratory occasions. In the early part of this century Niblock,[21] Fells[22] and Orr and Glasg[23] reported the association of betel quid chewing with oral cancer. The preponderance of cheek cancers was attributed to pan chewing.[2,24,25,26] Sanghvi[27] showed the association of tobacco chewing with oral cancer and the risk was reported to be 4-fold among chewers compared to non-chewers and non-smokers. A detailed case-control study was carried out by Jussawalla and Deshpande in 1971[28] and the study showed a 6-fold risk among chewers for oral cancer, a 3-fold risk for oropharyngeal cancer and a 5-fold risk for laryngeal cancer. Hirayama[29] carried out a survey in central and southeast Asia and showed strong supportive evidence for the association of oral and pharyngeal cancer with the chewing habit.

Table 7
Indian case-control studies on head and neck cancer –
Risk factors and RR estimates

Author and Year	Sites Studied	Sites Factors studied and Relative Risk			
		Chewing	Smoking	Chewing+ Smoking	Alcohol*
1. Sanghvi et al. (1955) Sanghvi (1981)	Oral Cavity/ Pharynx/Larynx	4.0	2.0 (Bidi)	4.0	-
2. Jussawalla & Deshpande (1971)	Oral Cavity	6.0	2.8	10.1	-
	Oropharynx	3.3	11.8	31.7	-
	Nasopharynx	1.8	3.3	4.8	-
	Hypopharynx	6.2	3.6	16.9	-
	Larynx	4.6	7.7	20.1	-
3. Reddy (1974)	Hard Palate	-	85.0 (males) / 132.0 (females)	Reverse Smoking	
4. Notani & Sanghvi(1976)	Oral Cavity	3.93	1.99	4.34	-
5. Notani & Jayant (1987)	Oral Cavity	3.9	5.2	7.6	-
	Pharynx	2.3	4.2	5.0	-
	Larynx	1.8	6.8	7.7	-
6. Notani (1988)	Oral Cavity	2.8	4.7	13.1	10.0–47.1
	Pharynx	2.1	4.5	9.3	11.6–50.2
7. Sankaranarayanan et al (1989-a)	Gingiva	4.1–13.2	2.0	16.0	1.9
8. Sankaranarayanan et al (1989-b)	Oral tongue and Floor of Mouth	6.1	5.0	7.0	-
9. Nandakumar et al (1990)	Oral Cavity	12.9	1.9	9.2	-
10. Rao et al (1994-a)	Oral Cavity	3.6	1.7	2.9	2.4–8.9
11. Rao et al (1994-b)	Oropharynx	2.2	7.9	5.5	7.0–9.6
	Hypopharynx	2.6	4.4	3.6	3.0–6.9

* *combined with other habits*

An IARC[30] monograph reported a dose-response relationship of the chewing habit with oral cancer. The risk was increased in betel quid chewers who chewed [illegible] in those who chewed more than 6 times a day compared to non-chewers.

Case control studies carried out in southern India demonstrated an excess relative risk among chewers for cancer in the gingiva, oral tongue, floor of the mouth and buccal mucosa.[31,32,33]

Recently, a hospital-based case-control study on male oral cancer was carried out at TMH, Bombay.[34] The study established that tobacco chewers had a 2.64 times excess risk for oral cancer. Chewing of betel quid with and without tobacco is also associated with oral and pharyngeal cancer.[28] Further, each individual ingredient in the quid such as betelnut alone, betelnut and tobacco, either alone or with smoking are also found to be associated with oral cancer.[30]

Risk estimates for chewing tobacco have been provided by many studies in the past, however the risk due to retention of the quid during sleep has not been estimated. Nandakumar

et al have shown that the risk estimates for quid retention versus non-retention during sleep were 17.7 and 8.5 times respectively.[33]

Khaini, Nass/Naswar, Masheri

Khaini, a mixture of a powder of dried tobacco leaf and lime is very popular in Bihar, India. As early as 1945, Khanolkar and Suryabai reported that the Khaini habit was associated with an excess risk of cancer of the labial mucosa.[35]

Nass and naswar are mixtures of tobacco, lime and other ingredients. They are used in the Soviet Republic, Pakistan and Afghanistan. A very high relative risk of 20.4 for oral cancer was reported among nass users and a risk of 14.2 among naswar users.[36]

Wahi in a study from Mainpuri district in Uttar Pradesh observed that the use of Mainpuri tobacco, a pre-prepared mixture of tobacco with lime and other ingredients elevated the risks for cancers of the buccal mucosa, gingiva and lip.[37]

Masheri (burnt tobacco) is used for cleaning the teeth in some parts of India. Mehta et al. carried out a prevalence survey in some parts of Maharashtra, India, and found the prevalence of this habit in approximately 20% of the population.[38] No oral cancer was detected among masheri users in this survey. The association of this habit with oral and pharyngeal cancer has to be established.

Smoking

In India, there are different smoking habits, viz. bidi smoking, cigar smoking, pipe-smoking, chutta smoking and the use of the hookah or chilum. The different methods of smoking are described by Sanghvi et al.[39]

An Indian cigar called 'Bidi', usually 60mm in length contains 0.2g - 0.3g of tobacco. It is sun dried, flaked and hand-rolled in tendu or temburni leaf (*Diospyros Melanoxylan*). Sanghvi et al[24] were the first to confirm the association of the tobacco habit, in particular bidi smoking with aerodigestive cancers.

Jayant et al[40] in an Indian study found that the dual habits, chewing and bidi smoking acted synergistically in the development of oral cancer. In fact, with the dual habit, a higher risk (31.72) was also noted for oropharyngeal cancer. In a recent case-control study conducted at TMH, Rao et al[34] confirmed the association of bidi smoking with oral cavity cancer.

A case-control study of male pharyngeal cancers seen at TMH showed a high risk among bidi smokers for oropharyngeal and hypopharyngeal cancer. Cigarette smoking did not emerge as

a significant risk factor. A dose-response relationship, both for duration and frequency of bidi smoking was also noted.[41]

Cigarette, cigar and pipe smoking is less popular in India. Rao et al[34] in their study did not find any excess risk for oral cancer among cigarette smokers but studies elsewhere found a positive association with oral cancer.[42,43,44] De Stefanni et al[45] studied the risk due to smoking of hand-rolled cigarettes and manufactured cigarettes. They found that smokers of hand-rolled cigarettes had an increased risk of cancer of mouth and pharynx cancers (RR=2.5) compared with smokers of manufactured cigarettes. The risk of laryngeal cancer was greater among hand-rolled cigarette smokers (RR=2.7).

Reverse Smoking

The habit of smoking by keeping the burning end in the mouth is practiced in the coastal districts of Andhra Pradesh, an eastern state of India. A local type of cigar, called the 'chutta' is used. The 'chutta' is a roll of dried tobacco leaf which is made into a small cigar and tied at one end with a piece of thin string. In Vishakapatnam, in the state of Andhra Pradesh, cancer of the hard palate is common.[35] Reddy and Kameshwara Rao[46] showed that the habit of reverse smoking of cigars was responsible for the high incidence of palatal cancer which was further supported by experimental work.[47] Reddy[48] reported an excess risk of 132 times in reverse chutta smokers for hard palate cancer in females compared to non smokers and a lesser risk in males (85.0). Another type of reverse smoking which is prevalent in Goa, western India, is 'Dhumti' smoking. Although no case of palatal cancer was observed in reverse dhumti smokers in a house to house survey,[49] there were marked keratotic changes in the palatal mucosa. Further studies are needed to assess the risk of cancer due to this habit.

A study conducted in Sweden and Colombia by Pindborg[50] revealed that reverse smoking was also reported to be a causal factor for base tongue cancer, a finding yet to be reported in India.

Snuff

Oral use of snuff (snuff dipping) is prevalent in India. Sankaranarayan et al[32] did not find any significant excess risk for oral cancer among snuff users in their study conducted in southern India but studies undertaken elsewhere confirmed the association with oral cancer.[51,52]

Cessation of tobacco habit

Information on cessation of habit, in particular for tobacco chewing and bidi smoking, was analysed in a case-control study on oral cancer.[31] RR estimates for ex-tobacco chewers and ex-bidi

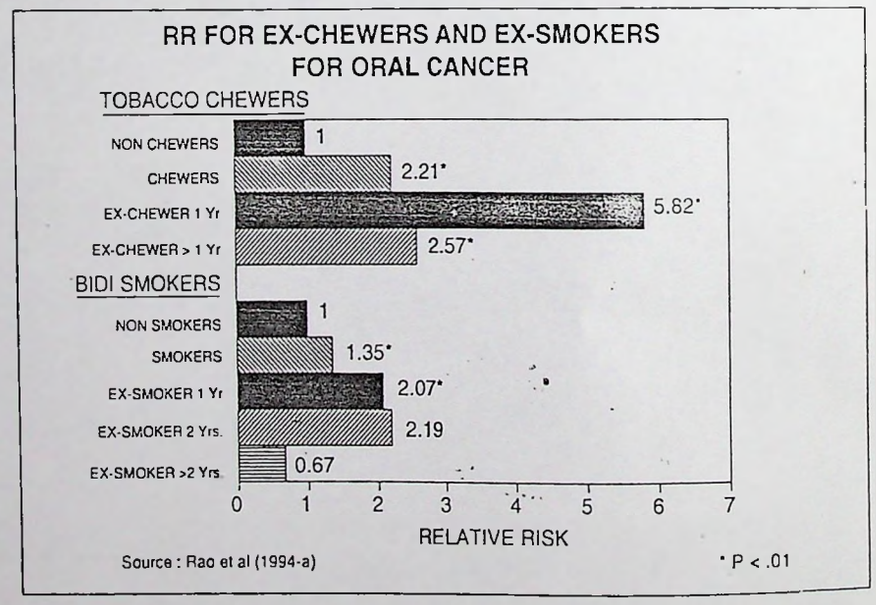
smokers are shown in Fig. 6. Although the relative risk for ex-tobacco chewers was reduced, it continued to be higher than non chewer controls. For bidi smokers however, there was a gradual reduction in the relative risk for ex-smokers with more than 2 years of cessation of smoking.

Alcohol

The social consumption of alcohol in India is not widely accepted. 'Country liquor' which is locally brewed, is the most common form of alcohol consumed. In general, persons indulging in this habit also have an added habit of chewing and/or smoking. Very few studies have been undertaken in India in the past to establish the role of alcohol in the etiology of oral and pharyngeal cancer.

Notani[54] showed that the alcohol habit when combined with chewing and/or smoking increased the risk for oral cancer. In males from a specific Hindu community, the risk of oral cancer was 10-fold among alcohol-chewers, 17-fold among alcohol-smokers and a very high relative risk of 47.1 among alcohol-chewers-smokers. In studies conducted in southern India, alcohol did not emerge as a risk factor for oral cancer[33,55]. Confirming the causal effect of smoking and alcohol in a recent case-control study on oral cancer, Rao et al[34] from India, showed that alcohol drinking emerged as a significant risk factor after adjusting for tobacco chewing and smoking (Fig. 7). The risk enhanced considerably when alcohol was also combined with chewing

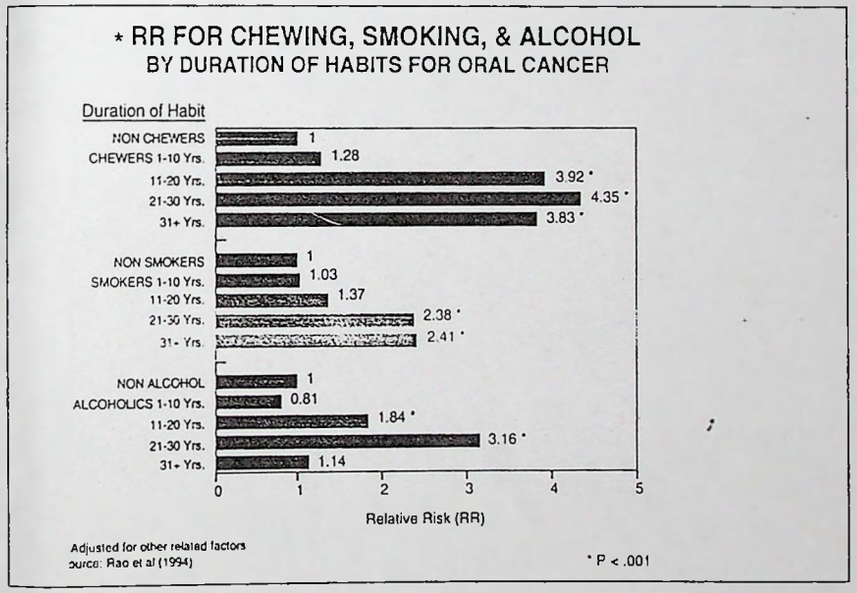
Fig. 6. RR for ex-chewers and ex-smokers for oral cancer.



(RR=4.3), and smoking (RR=2.4). The risk increased to 8.8 times for those with all the three habits (alcohol – chewing – smoking). This is in confirmation of the earlier study on the role of alcohol in oral cancer.[54] An increase in cancer risk with increase in duration of the alcohol habit was observed, with risk enhanced to 3.16 times for those who had the alcohol drinking habit for more than 20 years compared to non-alcohol drinkers (Fig 7). A case control study on pharyngeal cancer conducted at TMH has also revealed a positive association of alcohol with pharyngeal and laryngeal cancer. Further, the risk due to alcohol when combined with chewing and/or smoking, increased significantly.[41]

Case-control studies carried out in other parts of the globe have confirmed the association of alcohol consumption with oral and pharyngeal cancers.[56,57,58,59,60] In one of the earliest studies on alcohol, Wynder et al[44] provided the risk estimates of oral cancer due to alcohol consumption. A recent extensive review by the International Agency for Research on Cancer[53] on the role of alcohol in oral cancer concluded that epidemiological studies clearly indicate that drinking of alcoholic beverages is causally related to oral cancer and there is no indication that the effect is dependent on the type of beverage.

Fig. 7. RR for chewing, smoking, and alcohol: by duration of habits for oral cancer.



Diet

Table 8 gives some of the case-control studies undertaken to evaluate the association of dietary items with head and neck cancers. Excess use of red chilli powder in the diet emerged as

significant risk factor for oral, pharyngeal and laryngeal cancers and a significant dose-response relationship in terms of frequency was also observed.[61] An excess risk with consumption of salt-preserved meat and fish is reported for oral and pharyngeal cancer in a Chinese study.[57]

Table 8
Dietary risk factors in head and neck cancer

Author and Year	Factors Studied	Protective/Risk
1. Notani and Jayant (1987)	Pulses	Protective
	Vegetables	Protective
	Fish	Protective
	Buttermilk	Protective
	Fruits	Protective
	Groundnut oil	Protective
	Red chilli powder	Risk
2. Nandakumar et al (1990)	Ragi, a cereal diet	Risk
3. Zheng et al (1992)	Fruits	Protective
	Yellow Vegetables	Protective
	Chinese Radish	Protective
	Salt preserved fish	Risk
4. Rao et al (1994 a)	Non vegetarian	Risk
5. Kune et al (1993)	Fruits	Protective
	Vegetables	Protective
	Cereals	Protective

The rate of nasopharyngeal cancer was twice as high among the sea faring Tanka people, a sub ethnic group of Cantonese Chinese, than among land dwelling Cantonese and this was mainly attributed to the difference in dietary practices. The Tanka people usually added salted fish in their diet and rarely consumed citrus fruits.[62,63]

Rao et al[34] found a 39% excess risk among non-vegetarians for oral cancer after adjusting for other known associated factors. Hirayama[39] also found that among the non-vegetarians, the chewers had a 8-fold risk whereas among the vegetarians, chewers had only a 3-fold excess risk for oral cancer. It is also reported that non tobacco chewers who consumed ragi, a staple cereal diet (*Eleusine Coracana*, family *Graminae*), consumed by people in southern India, had 72.5 times excess risk for oral cancer and the risk level increased to 242.6 when ragi users also chewed tobacco.

Case-control studies on dietary items have shown that certain items play a protective role.[24,59,64] Notani and Jayant[61] found that consumption of certain vegetables and fish were protective factors for oral, pharyngeal and laryngeal cancer. In another study undertaken in China, a high intake of fruit, particularly oranges and tangerines, yellow vegetables and chinese radish decreased the risk for oral and pharyngeal cancer.

Experimental Studies

The etiologic role of betel-tobacco quid and bidi smoking in oral cancer was established experimentally. In animals, the implantation of a betel-tobacco quid pellet was shown to produce carcinomas in the cheek pouch of hamsters.[65] Chemical analysis of bidi smoke has showed presence of potent carcinogens like benzo(a)pyrene, etc.[66] Earlier, Hoffmann et al[67] gave a comparative chemical analysis of the Indian bidi and the American cigarette and stated that the way the bidi is smoked exposes the smoker in general to a higher level of noxious agents. Chemical analysis revealed that bidi smoke contained high concentrations of toxic carbon monoxide and other toxic agents in addition to a high concentration of particulate matter (tar) and the carcinogenic hydrocarbons, benz(a)anthracene and benzo(a)pyrene. The high temperature (760°C) in reverse smoking is believed to be an additional causal factor.[68]

Animal studies have demonstrated the mutagenicity of urine collected from rats fed with salted fish and these animals are prone to develop nasal cavity tumours.[69]

In a study carried out in India the presence of nitrosamines in smokeless tobacco products was found to be carcinogenic.[70]

Other risk factors

Dental and oral hygiene

Graham et al[71] showed that poor dentition increased the risk of oral cancer. In a recent study, Maier et al[72] showed that oral hygiene was affected with alcohol and tobacco consumption. Poor dental status and oral hygiene were observed in patients with head and neck cancer.[2] In a study from India[34], it was shown that illiterate people had a higher risk for oral cancer compared to literates. The factors that are generally associated with illiteracy like poor dental hygiene, under nourishment and low socio economic status, apart from the tobacco-habit, may be responsible for oral cancer. The pathogenetic mechanisms associated with these suspected risk factors remain to be investigated.

Occupational exposures

Male carpet installers and workers exposed to asbestos and petroleum products were found to be high risk groups for oral and pharyngeal cancer.[57]

An occupational study carried out in Nordic countries (Denmark, Sweden, Norway and Finland) demonstrated that for oral and pharyngeal cancer, an increased risk was found in male painters in Norway, Finland, and Sweden, whereas it could not be proved in Denmark.[73] In a

recent study conducted to determine whether pathologists with exposure to formaldehyde had an excess risk of cancer, particularly for cancer of the nasopharynx, failed to show any significance.[74]

Table 9
Summary of exposures associated with nasopharyngeal cancer

Exposure	Postulated Agent	Effect on risk
Epstein Barr Virus	Epstein Barr Virus	Increases
Diet		
Preserved foods	Nitrosamines	Increases
Fruits/Vegetables	Micronutrients	Decreases
Green Tea	Poly phenols	Decreases
Smoking	Nitrosamines	Increases
Smoke		Increases
Wood	Formaldehyde	Increases
Herbal medicines	Phorbol esters	Increases

Source : Hildesheim and Levine (1993)[42]

Virus etiology

Epidemiological studies on nasopharyngeal cancer carried out in high risk populations have brought out significant leads in the etiology of this cancer. Epstein Barr Virus has been identified and confirmed to be an causative agent in nasopharyngeal cancer. For other sites in head and neck cancer, a virus as a causative agent has not yet been confirmed. A list of exposures and their postulated agents along with the effect on risk is summarised in Table 9. The drinking of green tea and increased consumption of fruit and vegetables have been shown to be protective factors whereas daily consumption of preserved foods, use of herbal medicines, exposures to virus and smoking are known to increase the risk of nasopharyngeal cancer.

Chemoprevention

Chemoprevention is gaining ground and various products are under trial to evaluate their potential. Many studies are currently underway to identify the effect of beta carotene in reducing the risk of cancer among high risk populations. A recent study showed that leukoplakia responded to treatment with beta carotene but did not regress completely after treatment. The study concluded that beta carotene is the ideal candidate for potential use in the chemotherapeutic prevention of oral cancer.

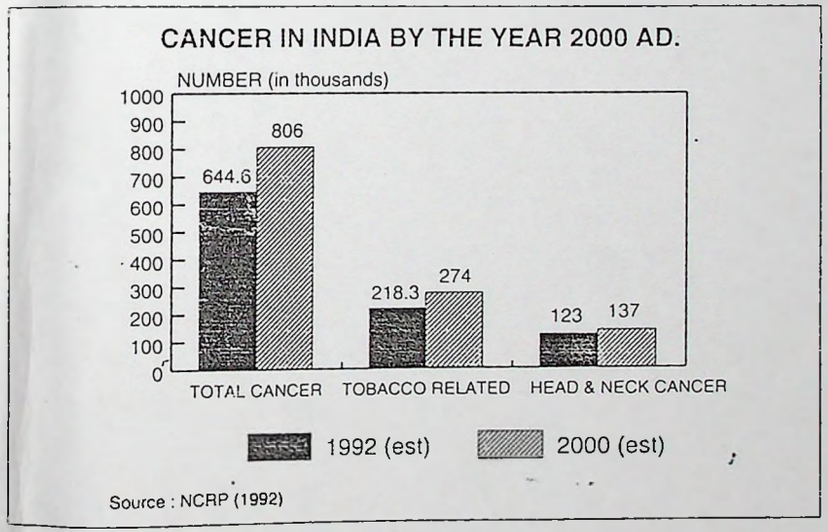
Cancer control

With the establishment of population based cancer registries in major metropolitan cities by the National Cancer Registry Programme of the Indian Council of Medical Research, New Delhi,

it has now been possible to identify the problem of cancer in the country and also common forms of cancer in Indian people. In 1992, an estimate of over 6,44,000 new cancer cases were diagnosed in the country. About 30-35% of these cases were mainly caused due to tobacco related habits. The present condition, if it continues, is likely to lead to a situation where by the year 2000 A.D., there will be over 8,00,000 new cancer cases per year in the country (Fig. 8).

In order to combat this problem, both the central and state governments have formulated cancer control programmes. Some of the important steps are: (a) a total ban on smoking in public and work environments and also on domestic air travel; (b) legislation to print the statutory warning about health hazards due to smoking on cigarette packets; (c) organization of mass screening programmes for head and neck cancer. Long term measures like mass public education on cancer and propagation of ill effects of tobacco among school children would also reduce the mortality due to cancer in the years to come.

Fig. 8. Cancer in India by the year 2000 AD.
Source: NCRP (1992).



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DIS-13-5

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RISK ASSESSMENT OF TOBACCO, ALCOHOL AND DIET IN CANCERS OF BASE TONGUE AND ORAL TONGUE - A CASE CONTROL STUDY

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SUMMARY

This is a retrospective case-control study of male tongue cancer patients seen at Tata memorial Hospital, Bombay, during the years 1980-84. The purpose of the study was to identify the association of tobacco, alcohol, diet and literacy status with respect to cancers of two sub sites of tongue namely anterior portion of the tongue (AT) (ICD 1411-1414) and base of the tongue (BT) (ICD 1410). There were 142 male AT patients and 495 BT patients interviewed during the period. 635 interviewed male patients who were free of any disease were considered as control. Bidi smoking was found to be a significant risk factor for BT patients and tobacco chewing for AT patients respectively. Alcohol drinkers showed about 45% to 79% excess risk for both sites of tongue cancer. Illiteracy and non vegetarian diet proved to be a significant factor for AT patients only. The study brings out that the location of cancer has got a direct bearing with the type of tobacco use and other related habits and this inturn may provide meaningful interpretation of variations observed in the incidence of tongue cancer around the world.

INTRODUCTION

Tongue cancer is generally an uncommon disease and its reported incidence is below 5 per 100,000 in about 135 populations / countries around the world[1]. In India, among 5 metropolitan registries the incidence rate of tongue cancer (ICD 141) in males varied between 4.7/100,000 in Bangalore and 13.2/ 100,000 in Bhopal[2] Clinical description, behaviour and management of tongue cancer depend on the location of the lesion, either in the base or in the oral tongue Tobacco chewing, smoking and alcohol habit were established risk factors for oral and pharyngeal cancer (ICD 140 -149) in general[3,4,5,6,7,8,9]. The purpose of the study is to identify the risk of these established factors with respect to two sites of tongue, namely base of the tongue (ICD 1410) and oral tongue (ICD 141-144) and its risk with respect to type of tobacco use.

PATIENTS AND METHOD

This is a part of the retrospective unmatched case-control study of head and neck cancer patients who attended the hospital during the period 1980-84. There were 713 male oral cancer patients and 1498 male laryngo pharyngeal cancer patients who were interviewed by two social investigators at the time of registration in the Out Patient Department. The patients were interviewed before clinical examination and thus investigators were not aware of the diagnosis of patients. Among them, 142 patients had cancer in anterior portion of the tongue and 495 patients had cancer in base of the tongue. During the period, there were 635 interviwed male patients who were diagnosed as being free from cancer, infections disease and benign lesion and these patients were classified as hospital control. Majority of the male controls

Table 1
General features of patients and controls

	Controls	(%)	Ant. Tongue (AT)	(%)	Base Tongue (BT)	(%)
1. Number	635		142		495	
Avg. Age+ S. D.	45.5 ± 12.9		49.1 ± 10.9		54.76 ± 9.7	
Range	25 - 87		27 - 75		29 -80	
2. Residence						
Bombay	386	60.8	56	39.4	186	37.6
Maharashtra	136	21.4	47	33.1	163	32.9
Others	111	17.5	38	26.8	146	29.5
Unkoown	2	0.3	1	0.7	-	
3. Religion						
Hindu Maharashtra	255	40.2	62	43.6	168	33.9
Hindu Gujarath	59	9.3	12	8.5	88	17.8
Sindhi	15	2.4	1	0.7	9	1.8
Hindu Others	150	23.6	39	27.5	119	24.0
Muslim	104	16.4	19	13.3	82	16.6
Christian	28	4.4	3	2.1	16	3.2
Other Religions	24	3.7	6	4.3	13	2.6
4. Habits						
No	175	27.6	23	16.2	36	7.3
Yes	460	72.4	119	83.8	459	92.7
5. Type						
Chewers	251	39.4	76	54.2	172	34.7
Smokers	295	46.8	69	49.3	404	81.6
Alcohol	122	19.4	39	28.2	113	22.8

whom we had considered for the study attended the hospital for complaints in head & neck region and later diagnosed to be of no evidence of disease or any abnormality. In general, chewers take pan, betal nut, lime and tobacco with some spices and condiments and smokers smoke Indian cigarette called bidis (obtained by wrapping 0.2g to 0.3g of tobacco in tendu leaf), cigarette, chutta (a kind of cigar) hukka and chilum (clay pipe). Bidi smoking and cigarette smoking are the commonest smoking habits. Factors considered for the study are tobacco usage (chewing and smoking) alcohol, mostly locally brewed from palm trees, (ethanol content 40%-60%), dietary habits (vegetarian / nonvegetarian) and literacy status. Vegetarians, in general do not consume poultry or fish products and avoid animal meat, The questionnaire included details of the habit, age started frequency per day and duration in years, and cessation of the habit. Unconditional logistic regression method was used to estimate the relative risk for factors. The relative risk estimates were obtained after stratification of factors by four age groups (<35yrs, 35–44 yrs, 45-54 yrs, 55 yrs+) and three areas of residence (Bombay, Maharashtra, Others).

RESULTS

General features like age, place of residence, religious distribution and habits of patients and controls are presented in Table I. The religious distribution of cancer patients and control did not differ and hence is not adjusted for in the analysis. Cancer patients and controls were in the age range of 25 years and 87 years. Base tongue cancer patients were found to be older about five years compared to anterior tongue cancer patients. Twenty three patients (16.2%) in anterior tongue (AT) group and 36 (7.3%) patients in base tongue (BT) group did not report any of the habits

Table II

RR estimates for chewers, smokers and alcohol users and tests of significance.*

Factors		controls	Ant. Tongue (AT)		Base Tongue (BT)	
			Case	RR	Cases	RR
A.	Chewers					
	Non Chewers	382	65	1.0	323	1.0
	Chewers	251	76	1.67 (1.12-2.51)	172	0.76NS (0.96-5.27)
	Not recorded	4	1		-	
B	Chewing Type					
	Non Chewers	382	65	1.0	323	1.0
	Tobacco Chewers	233	75	1.81 (1.21-2.73)	154	0.70 (0.5-0.9)
	Non Tobacco	11	0		14	1.32 NS (0.5-3.7)
	Others	5	1	0.67 NS (0.03-7.70)	4	0.60 NS (0.1-3.3)
	Not Recorded	4	1		-	
C.	Smoking					
	Non Smokers	336	72	1.0	91	1.0
	Smokers	295	69	0.97 NS (0.65-1.44)	404	4.34 (3.2-5.9)
	Not Recorded	4	1		-	
d.	Smoking Type					
	Non Smokers	337	73	1.0	91	1.0
	Bidi	186	53	1.12 NS (0.73-1.74)	360	5.90 (4.2-8.2)
	Cigarette	98	10	0.55 NS (0.24-1.15)	35	1.45 NS (0.9-2.5)
	Bidi + Cigarette	7	2	0.92 NS (0.12-5.43)	6	2.05 NS (0.5-8.4)
	Others	3	3	3.02 NS (0.44-21.3)	3	2.29 NS (0.3-19.6)
	Not Recorded	4	1		-	
e	Alcohol					
	Non User	509	102	1.0	382	1.0
	Alcohol User	122	39	1.79 (1.12-2.84)	113	1.45 (1.1-2.1)
	Not Recorded	4	1		-	

* - Stratified by 4 age groups and 3 areas of residence: NS - Not Significant
The figures in() indicate lower and upper Confidence Interval

considered in the study. Alcohol drinking was reported in 122 controls (19.4%), 39 (28.2%) patients in AT group and 113 (22.8%) patients in BT group. There was notable variation of habits with respect to two cancer groups. Among AT group, chewing habit was predominant (54%) whereas among BT group smoking habit was commonly observed (81%).

RR estimates for chewers, smokers and alchohol drinkers with confidence intervals are shown in Table II. Chewers had excess risk for anterior tongue cancer with relative risk (RR)1.81 (C.I. 1.2-2.7) whereas smokers had 4.3 times excess risk (C.I.3.2-5.9) for base tongue cancer. When categorised further, tobacco chewing emerged as a significant risk

Table III

RR for bidi smoking and use of alcohol and tests of significance according to frequency per day*

Factors		controls	Ant. Tongue Case	(AT) # RR	Base Tongue (BT)* Cases	RR
1.	Bidi					
	Non User	438	86	1.0	129	1.0
	1 - 10 times	79	25	1.23 NS (0.69-2.2)	141	4.32 (3.04 - 6.7)
	11 - 20 times	54	11	0.84 (0.78-1.78)	94	5.15 (3.39-8.5)
	21 - 30 times	56	18	1.39 NS (0.72-2.67)	107	4.8 (3.2-7.7)
	31 + times	4	1		24	14.3 (4.1-50.7)
	Not Recorded	4	1		-	
2.	Alcohol					
	Non User	509	102	1.0	382	1.0
	Once	108	27	1.46 NS (0.85-2.48)	99	1.51 (1.1-2.27)
	Twice	14	12	3.70 (1.69-10.8)	14	1.14 NS (0.44-3.1)
	Not Recorded	4	1		-	
3.	Tobacco					
	Non User	398	66	1.0	341	1.0
	1 - 10 times	203	67	1.88 (1.24-2.87)	135	0.7 (0.5-9.5)
	11- 20 times	28	7	1.65 NS (0.62-4.64)	14	0.5 NS (0.3-1.2)
	21 - 30 times	1	1	8.3 (0.12-391.3)	1	1.1 NS (0.03-45.1)
	31 + times	1	-		4	10.04 NS (0.5-209.40)
	Not Recorded	4	1		-	

+ - Stratified by 4 age groups and 3 areas of residence
- Trend Significant for tobacco and alcohol
* - Trend Significant for bidi and alcohol
NS - Not Significant; The figures in () indicate lower lower and upper Confidence Interval

for AT group only and bidi smoking was an important risk factor for BT group only. Cigarette smoking did not emerge as a significant risk factor for two sites. Alcohol drinking was found to be a significant risk factor for both subsites of tongue cancer and the estimated relative risk ranged between 1.45 and 1.79. Further the result of trend analysis with respect to frequency and duration of these habits for anterior tongue and base tongue cancers are separately shown in Table III and IV. The trend analysis again confirmed that the two habits namely bidi smoking and tobacco chewing showed statistically significant trends with the increse in the frequency and duration of the habits among BT and AT groups respectively. The trend analysis for duration of chewing habit was also statistically significant for anterior tongue cancer. Smokers who smoked bidi 31 times or more per day had about 14.3 times excess risk of getting base tongue cancer and the risk level for over 30 years of habit showed about 5 fold risk compared to non smokers. Cigarette smoking did not emerge as a risk factor for both groups either in terms of frequency or duration of the habit. The trend

Table IV

RR estimates + for bidi smoking and use of alcohol and tests of significance according to duration @

Factors	controls	Ant. Tongue Case	(AT) # RR	Base Tongue (BT)* Cases	RR
1. Bidi					
Non User	438	86	1.0	129	1.0
1 - 10 yrs	63	7	0.52 NS (0.2-1.3)	30	2.2 (1.3 - 4.1)
11 - 20 yrs	48	16	1.39 NS (0.7-2.7)	64	4.5 (3.1-8.7)
21 - 30 yrs	39	12	1.24 NS (0.6-2.8)	123	7.7 (4.8-13.0)
31 + yrs	43	20	1.61 NS (0.8-3.4)	149	5.1 (3.3-8.3)
Not Recorded	4	1		-	
2. Alcohol					
Non User	509	102	1.0	382	1.0
1 - 10 yrs	62	11	1.21 NS (0.6-2.6)	38	1.5 NS (0.9-2.5)
11 - 20 yrs	35	12	2.0 (0.9-4.4)	35	1.6 NS (0.9-2.9)
21 - 30 yrs	14	12	3.3 (1.4-8.9)	32	2.0 (1.0-4.6)
31 + yrs	11	4	1.3 NS (0.3-4.8)	8	0.5 NS (0.2-1.4)
Not Recorded	4	1		-	
3. Tobacco					
Non User	398	66	1.0	341	1.0
1 - 10 times	93	20	2.04 (1.04-3.86)	28	0.5 (0.3-0.89)
11- 20 times	51	25	3.58 (1.9-7.3)	31	0.9 (0.5-1.5)
21 - 30 times	48	19	1.83 (0.92-3.6)	47	0.9 (0.5-1.4)
31 + times	41	11	0.77 NS (0.33-1.77)	48	0.6 (0.4-0.99)
Not Recorded	4	1		-	

+ - Stratified by 4 age groups and 3 areas of residence
*@ - Trend Significant for tobacco & alcohol; *- Trend Significant for bidi & alcohol*
NS - Not Significant; The figures in () indicate lower and upper Confidence Interval

analysis for alcohol habit according to frequency and duration showed a statistically significant association with tongue cancer.

The literacy status and dietary factors were also analysed for the risk of these two sites after stratification by 4 age groups and 3 types of residence. The estimates were obtained without adjusting for tobacco and alcohol habits. Considering the risk among literate as unity, illiterates showed two fold risk (RR=2.1C. I.1.41-3.2) for AT cancer and 1.42 times excess risk (C.I. 1.08 - 1.93) for BT cancer. Patients who took non vegetarian diet were found to have two fold risk (RR =2.18C.I.1.27-3.84) for anterior tongue cancer only and for BT cancer there was a 34% significant reduction in risk with RR 0.66 (C.I. 0.48-0.89).

Table IV shows the unconditional logistic regression model for two cancer sites.

Table V

Unconditional logistic regression model using five factors for two sub sites of tongue*

Site / Factor	*RR*	*Confidence Interval*	*P Value*
Anterior Tongue (AT)			
Bidi (1=Yes; 0=No)	*1.0*	*0.66 - 1.52*	*p = 0.998*
Alcohol (1=Yeas; 0=No)	*1.54*	*0.97 -2.44*	*P = 0.063*
Illiteracy (1 = Yes; 0=No)	*1.81*	*1.198 - 2.73*	*p =0.005*
Nonvegerarian (1=Yes; 0=No)	*1.74*	*1.014 -2.995*	*P =0.044*
Tobacco Chewing (1= Yeas 0= No)	*1.74*	*1.173 - 2.571*	*P = 0.006*
Base Tongue (BT)			
Bidi (1=Yeas; 0=No)	*4.69*	*3.51 - 6.27*	*P <.001*
Alcohol (1=Yes; 0=No)	*1.34*	*0.93 - 1.93*	*P =0.116*
Illiteracy (1= Yes; 0=No)	*1.22*	*0.90 - 1.66*	*P = 0.195*
Nonvegetarian (1=Yes; 0=No)	*0.59*	*0.43 - 0.83*	*P = 0.002*
Tobacco Chewing (1= Yes; 0=No)	*0.88*	*0.65 - 1.19*	*P = 0.402*
Tongue (AT + BT)			
Bidi (1=Yes 0=No)	*3.32*	*2.56 - 4.3*	*p <.001*
Alcohol (1=Yes; = No)	*1.38*	*0.99 - 1.9*	*p = 0.05*
Illiteracy (1=Yes; 0=No)	*1.41*	*1.08 - 1.85*	*P=0.013*
Nonvegetarian (1=Yes; 0=No)	*0.77*	*0.56 - 1.04*	*P = 0.089*
Tobacco Chewing (1-Yes; 0=No)	*1.13*	*0.87 - 1.47*	*P = 0.36*

** - Adjusted for 4 age groups and 3 areas of residence*

The model confirmed the significance of tobacco chewing, nonvegetarian diet, and illiteracy status for anterior tongue cancer. Bidi smoking emerged as a significant risk factor for the base tongue cancer with RR 4.69 (C.I. 3.51-6.27). The risk due to alcohol habit was higher than unity in both sites but not found to be statistically significant in this multivariate model.

DISCUSSION

Epidemiological research in recent times has become possible to address issues to the specific sites of cancer according to International Classification of Diseases (ICD 9th). Data on cancer incidence are being reported with certain accuracy upto the fourth digit rubrics of ICD. This retrospective case control study was carried out to evalute the association of tobacco and alcohol habits with respect to cancer in the base and oral tongue. Only histologically confirmed tongue cancer cases were included in this study. Not all of the tongue cancer patients diagnosed during the period could be interviewed, for many reasons. Controls were chosen from among the interviewed patients who were diagnosed as being free from cancer, infectious diseases and benign neoplasms. The use of hospital controls instead of population controls may have affected the estimates of risk factors. Previous studies carried out in India, have identified risk factors for oral cancer (ICD 140-145) or for cancers of two or three sites of oral cavity[6,7,8,9,10]. In an earlier study from Bombay, the risk factors for individual sites of oral cavity, pharynx and larynx were analyzed and estimated but the study did not evaluate for alcohol and dietary factors[4].

The composition of habit pattern between control and cancer groups shows the predominance of smoking habit among BT group (81.6%) and chewing habit among AT group (54.2%). The study has brought out that the location of cancer in the tongue to some extent depends upon the type of tobacco habit. Bidi smokers in particualr had a higher rusk for

Base Tongue cancer than for Ant. Tongue cancer. The dose response relationship was also established according to frequency and duration of bidi smoking habit for BT cancer and tobacco chewing habit for AT cancer. When the two cancer groups were combined, the model showed significant association of bidi smoking, alcohol, and illiteracy with tongue cancer. Tobacco chewing and nonvegetarian diet did not emerge as significant.

The average age of the patients with respect to two cancer group show variation. This is also observed from the Cancer Registry data of the hospital for the last five years[11]. Patients with AT cancer were found to be about five years younger compared to BT cancer patients in the hospital data also. Further studies are required to identify factors responsible for this.

Alcohol as a high risk factor has been reported for oral cavity cancer in general. Previous studies showed that alcohol habit is associated with oral cancer[5,7]. In this study also it has been shown to be associated with AT cancer but not with BT cancer. It is necessary to collect more information on alcohol habit in our population and also the type of liquor and quantity consumed to provide a meaningful estimate of the risk involved with oral cancer and in general for all cancer.

Many studies have identified the role of dietary factors in cancer of mouth, pharynx and larynx. The association of dietary factors with oral cancer in particular has been confirmed in the studies conducted from India. Non vegetarian diet compared to vegetarian diet seemed to increase the risk for AT cancer. Further studies are required to assess the risk factors among individual items of nonvegetarian diet after controlling the known protective factors.

Illiterates had a higher risk for anterior tongue cancer in our study. This may be due to the different life style, habits and customs, poor socio economic status, dietary habits and poor oral hygiene among illiterates compared to literates. These factors need to be considered in future studies. It is necessary to have a new strategy for cancer control and prevention for such high risk groups.

In conclusion, the study brings out that the location of cancer has got a direct bearing with the type of tobacco use and other related habits and this inturn may provide meaningful interpretation of variations observed in the incidence of tongue cancer around the world.

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Survival analysis of 5595 head and neck cancers – results of conventional treatment in a high-risk population

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Summary This is a study of 5595 head and neck cancer patients treated during 1987–89 at TMH, Mumbai. The study included 1970 oral cancers (ICD 140–145), 1495 oropharyngeal cancers (ICD 1410, 1453, 146), 1255 hypopharyngeal cancers (ICD 148), 125 nasopharyngeal cancers (ICD 147) and 750 laryngeal cancers (ICD 161). The clinical extent of disease at presentation was based on TNM group staging (UICC 1978). For the majority of sites, patients attended the hospital during stage III and stage IV of the disease; the only exception was for cancers of the lower lip, anterior tongue and vocal cord when between 46.2% and 56.5% of patients with localized cancer (stage I and II) were seen. Generally, surgery either alone or with radiation has been administered for oral cancer patients whereas radiation either alone or in combination with chemotherapy was administered for other head and neck sites. The overall 5-year survival rate was in the range of 20–43% for oral cancer, 8–25% for pharyngeal cancers and 25–62% for laryngeal cancer. The 5-year relative survival rates were more or less in agreement with the results published by the Eurocare study for head and neck cancers. The importance of primary prevention in head and neck cancer is stressed.

Keywords: head and neck cancer; survival; TNM; stage; treatment

Incidence data that are available from six metropolitan cities and one rural registry in India indicate that head and neck cancer is a common problem there (IARC, 1992). Many epidemiological studies carried out in the sub-continent have shown the association of tobacco, alcohol and some dietary items with head and neck cancer. Although primary prevention may be the ideal choice for the control of head and neck cancer, secondary prevention through therapeutic intervention has an equal and important role to play. Management of head and neck cancer in a high-risk population and its response to conventional treatment and survival have not been reported in detail. The aim is to analyse individual sites of head and neck cancer according to stage of the disease, primary treatment and other prognostic factors for 5-year survival. Comparison is also made with survival in European countries.

PATIENTS AND METHODS

This is a retrospective analysis of 5595 eligible head and neck cancer patients who were diagnosed and treated at Tata Memorial Hospital, Mumbai, during the period 1987–89. The eligibility criteria for inclusion of patients in the study were: (1) no prior cancer-directed treatment at the time of registration; (2) histologically confirmed epithelial cancer; (3) treatment with chemotherapy together with surgery or radiation but not as the only treatment; and (4) at least 50 cases in each subsite of head and neck cancer. The excluded subsites were upper lip (five cases), commissure of lip (six cases), tongue NOS (not otherwise specified) (one case), salivary gland (39 cases), palate NOS (two cases) and subglottic larynx (seven cases). Information on age, sex, date of diagnosis, method of diagnosis, primary site (ICD 1978), secondary site, if available, histology of primary and/or secondary tumour, TNM staging (UICC, 1978) and primary treatment given within 6 months of diagnosis were obtained from the database maintained by the hospital cancer registry. The clinical extent of the disease for head and neck cancer cases was classified into four stages, viz. stage I comprising $T_1N_0M_0$ status, stage II comprising $T_2N_0M_0$, stage III comprising $T_3N_0M_0$, $T_3N_1M_0$, $T_1N_1M_0$ and $T_2N_1M_0$ and stage IV comprising $T_4N_0M_0$, $T_4N_1M_0$, and any T, N_2 or N_3M_0 and any T any N M_1. Periodic updating of follow-up information was carried out either by scrutiny of medical records of attending patients or by postal enquiry responses. In some cases, follow-up information was also obtained by scrutiny of death records maintained by the Municipal Corporation of the City, of life insurance claims and of records from terminal care centres/pain clinic in the city. The study was closed on 31 March 1996, and data available up to that time were used for the survival analyses. In this study of 5595 patients, 2435 patients (43%) were known to have died and 1128 patients (20%) were known to be alive at the end of 5 years from their date of diagnosis. For the remaining 2032 patients, 267 patients (4.7%) had follow-up information for between 3 and 5 years, 1384 patients (24.7%), categorized as non-responders, had less than 3 years of follow-up information and 381 patients (6.8%) had incomplete addresses (untraced cases). Complete follow-up information was 68% for the laryngeal group, 65% for oral cancer, 64% for the oropharyngeal and nasopharyngeal group and 60% for the hypopharyngeal group. At the end of 1 year, the equivalent figures were about 84% for laryngeal cancer and 70–80% for the other groups.

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Table 1 Clinical characteristics and observed survival rates (%) for oral cancers 1987–89

Site (ICD 9)	Lower lip (1401)	Ant. tongue (1411–14)	L. alveolus (1431)	U. alveolus (1430)	Floor mouth (1449)	Buccal mucosa (1450–51)	Hard palate (1452)	Retromolar (1456)
Number of cases	62	522	340	71	88	728	90	69
Sex ratio	3.1:1	2.3:1	2.3:1	1.7:1	7.8:1	2.2:1	3.3:1	2.8:1
Average age ± s.d. (years)	50.7 ± 13.6	49.4 ± 11.9	52.2 ± 10.5	52.7 ± 13.6	51.1 ± 9.4	50.8 ± 11.7	54.1 ± 12.5	53.2 ± 9.2
Stage (%)								
I	22.6	20.9	1.2	2.8	5.7	6.2	1.1	1.5
II	32.3	25.3	6.7	19.7	18.2	20.0	26.6	13.0
III	14.5	31.0	9.1	47.9	13.6	19.5	36.6	30.4
IV	29.0	21.3	81.2	22.5	58.0	52.1	17.9	53.6
NOS	1.6	1.5	1.8	7.1	4.5	2.2	17.8	1.5
Treatment summary (%)								
Surgery	83.9	50.4	48.8	32.4	23.9	42.9	18.9	23.2
Radiation	1.6	18.8	6.5	21.1	36.4	19.1	56.7	39.1
Surgery + radiation	12.9	22.4	35.3	39.4	28.4	28.7	20.0	24.6
Others*	1.6	8.4	9.4	7.1	11.3	9.3	4.4	13.1
Survival with CI								
1 year	61 (49–73)	55 (51–59)	62 (57–68)	46 (35–58)	47 (36–57)	61 (57–64)	51 (41–61)	56 (45–68)
3 years	48 (36–60)	36 (32–40)	35 (30–40)	21 (12–31)	23 (14–31)	39 (35–42)	34 (25–44)	29 (18–40)
5 years	43 (31–56)	33 (29–37)	31 (26–36)	20 (10–29)	21 (13–30)	34 (31–37)	31 (21–40)	25 (14–35)
Median survival (in months)	33	17	19	12	12	20	16	17

*Includes chemotherapy either with surgery or with radiation or with both. CI, 95% confidence interval; NOS, not otherwise specified.

Table 2 Clinical characteristics and observed survival rates (%) for pharyngeal and laryngeal cancers 1987–89

Site (ICD 9)	Base tongue (1410)	Soft palate (1453)	Tonsil (1460)	Oropharynx NOS (1461–69)	Post cricoid (1480)	Pyriform fossa (1481)	Hypopharynx NOS (1482–89)	Vocal cord (1610)	Supra glottic (1611)	Nasopharynx (1470–79)
Number of cases	818	142	346	189	171	1000	84	259	491	125
Sex ratio	11.4:1	7.4:1	8.6:1	6.3:1	0.9:1	12.3:1	3.4:1	17.5:1	7.8:1	4.2:1
Average age ± sd (years)	55.0±10.6	56.2±10.5	55.9±10.9	56.6±10.5	49.9±13.9	55.5±10.4	53.6±13.5	56.0±11.2	55.2±10.5	38.2±18.2
Stage distribution (%)										
I	0.7	6.3	2.0	2.1	1.2	0.1	1.2	51.7	1.8	0.8
II	10.1	25.4	8.1	13.2	15.2	8.7	11.9	15.4	11.4	2.4
III	46.2	38.7	50.6	55.0	50.9	52.9	60.7	20.1	56.0	15.2
IV	41.7	27.5	37.3	28.0	29.8	37.0	25.0	9.7	25.7	76.8
NOS	1.3	2.1	2.0	1.7	2.9	1.3	1.2	3.1	5.1	4.8
Treatment summary (%)										
Surgery	0.7	2.1	0.3	0	10.5	3.4	2.4	11.2	2.9	0
Radiation	86.2	81.7	87.3	90	74.3	79.1	84.5	74.9	85.7	50.4
Surgery + radiation	3.2	6.3	2.9	2.1	11.1	12.9	4.8	13.1	8.6	4.8
Others*	9.9	9.9	9.5	7.9	4.1	4.6	8.3	0.8	2.8	44.8
Survival with CI										
1 year	43 (39–46)	58 (49–66)	44 (39–49)	45 (38–52)	34 (26–40)	48 (44–51)	39 (29–50)	82 (77–87)	54 (41–58)	50 (42–59)
3 years	19 (16–21)	33 (25–41)	15 (11–19)	20 (14–26)	16 (11–22)	22 (19–24)	13 (6–20)	65 (59–71)	28 (24–32)	27 (19–35)
5 years	15 (12–17)	25 (17–32)	13 (9–16)	14 (8–19)	13 (8–18)	17 (15–20)	8 (2–14)	62 (56–68)	25 (21–29)	21 (14–28)
Median survival (in months)	10	18	11	11	7	12	9	*	14	13

*Includes chemotherapy either with surgery or with radiation or with both. *Not reached. CI, 95% confidence interval; NOS, not otherwise specified.

The number of untraced cases was around 7% for all sites, except laryngeal cancer for which the figure was 3.7%; similarly, the proportion of non-responders was around 25% for all sites except for laryngeal cancer (21.6%). The proportion of both untraced and non-responding patients who had stage III and stage IV cancers at their first visit to hospital was between 70% and 92% in the different site groups, and these patients were considered unsuitable for further treatment, except for pain relief or symptomatic treatment. Patients with less than 3 years of follow-up were considered as being deceased, and survival information available up to that time was used for analysis purposes. The Kaplan–Meier method was used to estimate survival rates for 1, 3 and 5 years and also to assess certain prognostic factors considered in the study. As 70% of the patients attended hospital from Maharashtra state, the life table for Maharashtra State, published by the Government of India for the period 1986–90 (RGI, 1994), was used to estimate the relative survival rates.

Table 3 Five-year observed survival rates (in %) for oral cavity, pharyngeal and laryngeal cancers by treatment

Site	Surgery	Radiation	Surgery + radiation	Surgery + chemotherapy	Radiation + chemotherapy	Surgery + radiation + chemotherapy
Oral cavity						
Lower lip	47.8	0[a]	25	–	–	0[a]
Anterior tongue	47.8	13.2	22.0	33.3	11.1	27.2
Lower alveolus	34.4	13.6	28.9	45.0	20.0	14.3
Upper alveolus	30.4	13.3	17.1	–	0[a]	0[a]
Floor mouth	42.9	3.1	36.0	–	–	0[a]
Buccal mucosa	46.4	23.3	27.9	30.7	6.7	26.3
Hard palate	58.8	19.6	38.9	–	25.0	–
Retromolar	37.5	14.8	41.2	0[a]	0[a]	0[a]
Oropharynx						
Base tongue	66.7	15.3	19.2	0[a]	6.0	0[a]
Soft palate	66.7	24.2	55.6	–	–	0[a]
Tonsil	0[a]	13.9	20.0	–	3.3	0[a]
Oropharynx NOS	–	14.0	0[a]	–	7.1	100[a]
Hypopharynx						
Post-cricoid	11.1	14.8	7.9	–	0	0[a]
Pyriform fossa	14.1	15.6	32.5	0[a]	7	100[a]
Hypopharynx NOS	0[a]	8.5	0[a]	–	–	–
Nasopharynx	–	12.7	44.4	–	28.5	0[a]
Larynx						
Vocal cord	72.4	62.1	51.7	–	50.0	–
Supraglottic	28.6	25.2	48.0	0[a]	25.0	0[a]

[a]Estimate based on five or less cases. –, No patient.

Table 4 Five-year relative survival rates (%) according to sex and TNM group staging for head and neck cancers 1987–89

	Five-year relative survival (%)					
	Sex		Stage			
	M	F	I	II	III	IV
Oral Cavity						
Lower lip	51.3	35.6	69.8	54.0	60.3	12.7
Anterior tongue	35.5	35.8	63.6	49.8	22.8	11.2
Lower alveolus	36.2	29.5	56.0	65.6	41.7	30.0
Upper alveolus	24.8	16.5	0[a]	31.2	19.4	13.5
Floor mouth	20.8	42.6	65.2	33.7	26.6	14.9
Buccal mucosa	39.4	32.1	67.4	60.6	25.3	25.0
Hard palate	35.3	30.4	100	49.6	23.3	7.0
Retromolar	30.6	18.0	100[a]	36.7	31.3	17.6
Oropharynx						
Base tongue	16.64	16.6	89.94	35.8	21.2	4.94
Soft palate	26.2	38.8	50.2	39.6	27.9	8.77
Tonsil	14.95	12.1	64.1	30.8	14.37	8.3
Oropharynx NOS	15.3	15.7	0[a]	50.8	10.3	8.3
Hypopharynx						
Post-cricoid	15.5	12.7	0[a]	36.4	13.5	2.1
Pyriform fossa	19.9	17.25	0[a]	44.6	21.8	10.8
Hypopharynx NOS	8.6	11.3	100[a]	0	10.7	5.2
Nasopharynx	21.6	23.7	100[a]	35.5	22.7	21.7
Larynx						
Vocal cord	70.45	60.36	78.9	60.5	55.6	52.0
Supraglottic	27.2	38.0	74.0	61.7	28.7	9.1

[a]Estimate based on five or less cases.

RESULTS

The clinical characteristics, TNM staging, treatment summaries and observed survival rates for 1970 oral cancer cases are presented in Table 1. The average age of patients ranged from 49.4 years for anterior tongue cancer to 54.1 years in hard palate cancer. The distribution of TNM staging among eight sites of oral cancers showed that except for lower lip (54.9%) and anterior tongue

cancer (46.2%), for most of the sites, patients with stage I and stage II disease together accounted for between 7.9%, for lower alveolus cancers, and 27.7%, for hard palate cancers.

Management of oral cancer depends largely on the stage of the disease. In our series, surgery alone or radiotherapy alone or their combination remained as the primary treatment. The 'other' treatment category mostly included the combination of chemotherapy with either surgery or radiation or both in the management of oral cancer. The 5-year observed survival rate varied between 20% for the upper alveolus and 43% for lower lip cancers.

The comparable data for pharyngeal and laryngeal cancers are presented in Table 2. In contrast to most of the cancers, a marked predominance of men was seen for all the sites except for post-cricoid cancers, for which a female excess was observed. The average age of the patients varied between 38.2 years for cancer of the nasopharynx and 56.6 years for oropharyngeal cancer. The base of the tongue (818 cases) and pyriform fossa (1000 cases) were the two predominant sites observed in this group. The TNM stage distribution of individual sites indicated that 80–90% of cases presented with stage III or IV malignancies, the only exception being for vocal cord cancers for which the percentage was much lower (30%). In view of this, for most of the patients, radiotherapy was administered as the only treatment. In the case of nasopharyngeal cancer, radiation along with chemotherapy was administered for about 44.8% of the patients and the 5-year observed survival rate for vocal cord cancer was about 62%. For all other sites, the 5-year survival rate ranged between 8%, for hypopharyngeal cancers, and 25%, for both soft palate and supra glottic cancers.

The 5-year observed survival rates according to primary treatment for the eighteen sites of head and neck cancer considered are presented in Table 3. Surgery, when used alone for the treatment of oral cancer, was followed by a 30–58% 5-year survival of patients. The 5-year survival for radiotherapy alone in oral and pharyngeal cancers in our study was in the range of 3–24%. Vocal cord cancer, when treated by radiotherapy alone, showed a 62% 5-year survival rate. The certain combinations of treatment showed good percentage 5-year survival rates for particular sites, namely nasopharynx, lower alveolus and supra glottis.

The 5-year relative survival rates by sex and TNM stage for all the 18 sites of head and neck cancer are presented in Table 4. Women showed better 5-year survival rates for cancers of the floor mouth (M, 20.8%; F, 42.6%), soft palate (M, 26.2%; F, 38.8%) and hypopharynx (M, 8.6%; F, 11.3%) than men. The stage of the disease is known to be an important prognostic factor. With the increase in the stage of disease, there has been a corresponding decrease in survival. Although few patients were observed with

Table 5 Five-year relative survival rates (%) for the Eurocare study (A) and the Tata Memorial Hospital Study (B)

(A)					(B)		
	Eurocare study[a] Study period 1978–85				Hospital study Study period 1987–89		
			Country (%)				
Site (ICD)	Cases	5-year survival	Highest	Lowest	Site (ICD)	Cases	5-year survival
Tongue (141)	3299	39	Scotland (46) Finland (45) Switzerland (43)	Poland (15) France (28) The Netherlands (28)	Tongue[b] Base tongue Anterior tongue	1341 818 522	24.02 16.6 35.8
Oral cavity (143–145)	4382	46	The Netherlands (62) Finland (51) England (48)	Estonia (33) Poland (33) Italy (38)	Oral cavity[c] Upper alveolus Lower alveolus Floor mouth Buccal mucosa Hard palate Soft palate Retromolar	1529 71 340 88 728 90 142 69	33.2 21.7 34.3 23.4 37.3 34.4 27.6 27.0
Oropharynx (146)	2457	33	The Netherlands (45) Poland (44) England (36)	Italy (23) Scotland (23) Estonia (27)	Oropharynx Tonsil Oropharynx	535 346 189	14.7 14.6 15.4
Nasopharynx (147)	1078	38	Switzerland (84) Italy (55) Finland (51)	Estonia (16) Scotland (24) Poland (28)	Nasopharynx	125	22.2
Hypopharynx (148)	2199	19	The Netherlands (36) Scotland (24) Estonia (23)	Poland (7) Finland (8) Switzerland (14)	Hypopharynx Post-cricoid Pyriform fossa Hypopharynx	1255 171 1000 84	18.0 14.3 19.6 9.2
Larynx (161)	10 612	57	The Netherlands (73) Scotland (64) England (63)	France (47) Estonia (50) Denmark (60)	Larynx[d] Vocal cord Supraglottis	757 259 491	41.8 68.0 28.0

[a]Source, IARC (1995). [b]Includes tongue NOS (one case). [c]Includes palate NOS (one case). [d]Includes subglottis (seven cases).

stage I cancer, the 5-year relative survival rates were in the range 56–100% for oral cancers (except for the upper alveolus), 50–90% for oropharyngeal cancer, 100% for nasopharyngeal cancer and 74–79% for laryngeal cancer. This indicates the effectiveness of conventional treatment in the early stage of the disease.

DISCUSSION

This is a retrospective analysis of 5595 head and neck cancer patients treated during the period 1987–89. Some other sites, namely upper lip, nasal sinus, max antrum and salivary glands, were not included mainly because of the small number of cases and/or because non-epithelial cancers were prevalent among these sites. Management of head and neck cancer depends largely on the size of the tumour, nodal status and histological variety. For oral cancer, surgery either alone or in combination with radiation had been the modality of treatment. For oropharyngeal and hypopharyngeal cancers, radiation therapy had been administered, largely because of the advanced stage of the disease at presentation. In the case of nasopharyngeal cancer, chemotherapy had been administered along with radiation therapy in a large percentage of cases. Laser surgery had been performed for a few selected sites of head and neck cancer but was not identified separately in our analyses. The sequence of treatments, when more than one was administered, has not been considered. In addition, no attempt has been made to identify the nature of surgery or level of radiation dose or chemotherapy schedule in evaluating the efficacy of the treatment. Furthermore, statistical comparison has not been made of the efficacy of different treatments from the data presented in Table 3, mainly because of the likehood of selection bias and of patients' reluctance to undergo surgery, which often would have involved reconstruction and a long stay in hospital. In this study, we have not looked at disease-free survival to indicate the efficacy of primary treatment for head and neck cancer, and many of the patients during the course of follow-up may have received treatment for recurrences or for metastatic disease that subsequently prolonged their survival; in which case, primary treatment alone cannot be considered to have cured the disease.

In general, among the patients considered for the study, 25% came from the city of Mumbai, about 45% from the State of Maharashtra and the rest from various states in India. Cancer is not a notifiable disease and vital statistics records for various states in India do not provide the cause of death. Patients' follow-up status was ascertained mainly through postal inquiry. Non-availability of complete addresses for the patients and failure to respond to our postal inquiry are the factors responsible for a significant percentage of loss during the first year of follow-up in our study. However, the assumption that patients lost to follow-up by the end of 3 years were dead is probably reasonable given that the majority had stage III or IV cancers the last time that they were seen.

The results of the present study are compared in Table 5 with those from the Eurocare study (IARC, 1995). In our study, the results are available for subsites of all head and neck cancers (fourth digit ICD), whereas in the Eurocare study some sites are only available by three-digit site (e.g. 141 – tongue) or by combinations of three-digit codes, as in the case of oral cavity (ICD 143–145). To facilitate comparisons, grouped results are also given for the Indian data in Table 5, including here the small number of subsites that were excluded from the main body of the study. Although the 5-year survival rates show distinct variation between the sites and subsites, the results obtained in our study are reasonably similar to those observed in the Eurocare study. The importance of reporting survival by subsites is clearly brought out in the case of tongue, oral cavity and pharynx.

Other studies have been reported in the literature either for all sites of head and neck cancer individually or by groups (Flores et al, 1986; Rice and Spiro, 1989; Steinhart and Leinsassaer, 1992; Cole et al, 1994; Sagar et al, 1994; Mishra et al, 1996; Mohanti et al, 1996; Grau et al, 1997). The direct comparison of our study results with those reported in the literature has to be done with caution, however, especially as the majority of studies report observed rather than relative survival rates.

Head and neck cancer constitute about one-third of all cancer seen at Tata Memorial Hospital, Mumbai. The TNM staging distribution of head and neck cancer in the hospital over the years indicates that a high percentage of cases were seen at an advanced stage of the disease (HCR, 1996). The present study also showed a large percentage of patients with advanced disease at presentation. This, in turn, is reflected in the low survival rates observed for some sites of head and neck cancer in comparison with those seen in European countries.

Many epidemiological studies carried out from high-risk and low-risk populations have indicated the association of tobacco, alcohol, the chewing of betel quid and some dietary items with head and neck cancer. Eventually, head and neck cancer control will best be achieved through primary prevention, although earlier diagnosis should also be an aim.

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EPIDEMIOLOGICAL OBSERVATIONS ON CANCER OF THE OESOPHAGUS - A REVIEW OF INDIAN STUDIES

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SUMMARY

This is an epidemiological review on cancer of the oesophagus. In this attempt, all aspects of epidemiological factors based on national and international studies on oesophageal cancer have been brought out. The problem of this cancer in Indian context has been documented. The association of tobacco and alcohol habits with oesophageal cancer has been confirmed from the studies conducted in India. There is an urgent need to educate the common people about the harmful effect of these two habits and governments and voluntary organisation should take effective steps for its prevention.

Extensive epidemiological studies carried out on cancer of the oesophagus have highlighted the peculiarity of the disease, high and low incidence being reported in the same country and in some instance in geographical areas in the country separated by few square kilometers.

Cancer of the oesophagus has evinced a great interest among clinicians and epidemiologists for a long time. A rapid stride in the diagnostic techniques and increased rate of microscopic confirmation of the disease, and use of adjuvant chemo-theraupetic management have not made great dent in the survival rate. Epidemiologists all over the world have paid greater attention to identify the etiology of the disease and thereby pave way for its prevention.

In this review, an attempt has been made to provide bird's eye view of epidemiological observations on cancer of the oesophagus in the subcontinent, its incidence and mortality, trends, high risk groups and associated tobacco habits and dietary factors.

Clinical Epidemiology

The disease is known to occur, in general, among elderly people. The average age of oesophageal cancer is about 52 years[1]. The disease is predominant among males compared to females but in areas of high incidence, the rates in females may exceed those in males. With the advent of Fine Needle Aspiration Cytology and endoscopic biopsy, diagnostic confirmation of this disease has increased substantially over the decades. At present over 90% of cases are microscopically confirmed. Squamous carcinoma is the commonest histological type seen in most of the hospital series. Adenocarcinoma has been reported in 7% of cases.

At the Tata Memorial Hospital, Bombay, oesophageal cancer accounted for 9-11% of all cancers in 1970's whereas at present it is about 6-7% of all cancer cases. Generally around 700-800 cases are

diagnosed annually. Fig. 1 shows the relative proportion of oesophageal cancer seen in three cancer hospitals and three general hospitals in the country[2]. High percentage of oesophageal cancer (15%) was observed in Dibrugarh Cancer Registry, Assam, north-eastern part of India and low percentage (4%) in Trivandrum Cancer Registry, Kerala, the southern tip of India. Among the cancer hospitals, the percentage varied from 6.2% in Madras to 8.5% in Bangalore.

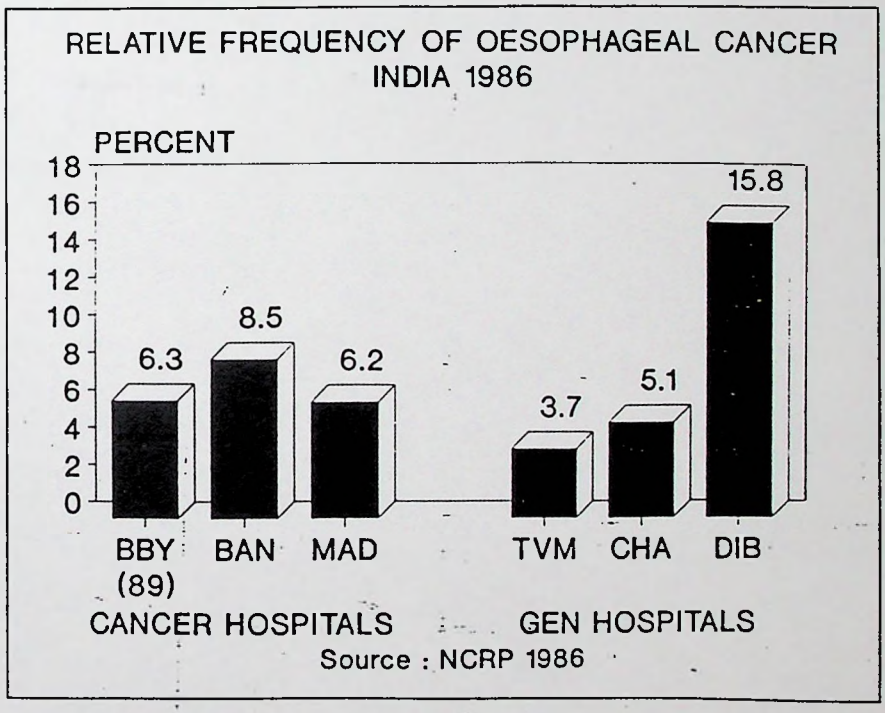

Fig. 1

Segment Distribution

At the Tata Memorial Hospital, Bombay, 2898 oesophageal cancer cases were recorded among 46,243 total cancer seen during the three year period 1989-91 [1,3,4]. This accounted for 46.3% of digestive tract cancers and 6.3% of total cancer. Distribution of cases according to segment of oesophagus as seen in six hospital cancer registries [1,3,4,5] is shown in Table I. At TMH, Bombay, cancer in the middle third of oesophagus accounted for 52.8% of cases followed by lower third (31.1%) and upper-third of oesophagus (11.7%). The sex ratio did not show any variation in the different segments of oesophagus, maintaining almost two males to one female ratio. Cancer was more often seen in middle third of the oesophagus in all cancer registries except in Madras where higher percentage of cancer was seen in lower third of the oesophagus.

Table I

Segment Distribution of Oesophageal Cancer Among Six Hospital Cancer Registries in India

Segment	Bombay+		Madras*		Bangalore*		Trivandrum*		Dibrugarh@		Chandigarh*	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Cervical Oes.	60	2.1	13	4.7	-		-		-		-	
Upper 1/3rd Oes.	341	11.7	18	6.5	46	9.0	18	11.4	122	12.7	14	11.5
Middle 1/3rd Oes.	1530	52.8	88	31.9	249	48.7	78	49.4	469	48.7	58	47.5
Lower 1/3rd Oes.	901	31.1	110	39.8	88	17.2	44	27.8	229	23.8	39	32.0
Oesophagus NOS	66	2.3	16	5.8	126	24.7	7	4.4	-		-	
Oesophagus Others	-		31	11.3	2	0.4	11	7.0	142	14.8	11	9.0
	2898		276		511		158		962		122	

Reference : + - *1, 3, 4;* * - *2;* @ - *5*

Maharashtra State

In order to assess the magnitude of problem of this cancer in the state of Maharashtra, the two available sources, namely hospital data and population based registry data are used. In the State of Maharashtra there are, apart from Bombay registry, population based registries in Pune and Nagpur and a rural registry in Barshi, Sholapur. The age standardised rates for oesophageal cancer in Pune during 1978-82 were 14.5 per 10^5 for males and 12.4 per 10^5 for females and in Nagpur during 1980-82 the incidence rates were 14.3 per 10^5 and 9.1 per 10^5 for males and females respectively [6]. Even in Barshi, a rural registry with a population of about 3,82,904 persons covering 346 vilages, oesophageal cancer incidence rate in 1989 was about 6.7 per 100,000 in males and 1.4 per 100,000 in females [7].

Annually about 5000 cancer patients from the Maharashtra state (excluding Bombay) attend the Tata Memorial Hospital, Bombay. In order to assess the magnitude of cancer, the State of Maharashtra has been broadly divided into six regions, namely, Konkan - the coastal areas of Arabian sea, northern part of Bombay as Khandesh, central part as Western Ghats and Marathwada, and the eastern part as Vidharbha and the remaining part as South Maharashtra. The region wise attendance of cancer patients during the period 1989-91 at the Tata Memorial Hospital indicate that the relative frequency of oesophageal cancer varies from 6% of all sites in Western Ghats to 9.7% in Vidharbha region (Table II).

Available data from metropolitan registries and rural registry indicate that oesophageal cancer is common in the State.

Incidence - National Scene

The earliest country-wide estimate of incidence data was reported from the survey of cancer cases in different railway zones in 1967. The average annual incidence

rates per 100,000 for major sites in gastrointestinal tract are shown in Fig. 2. High incidence of oesophageal cancer was observed in western zone which included Bombay and Gujarat states and stomach cancer in southern zone [8].

With the establishment of population based registries, it has become possible to obtain incidence of cancer in selected metropolitan cities in India. The age-adjusted incidence rates per 100,000 for cancer of the oesophagus reported from five metropolitan cancer registries and some selected countries published in Cancer Incidence in Five Continents Vol V and VI are shown in Fig. 3 [6,9]. There are variations

Table II

Digestive Cancers at Tata Memorial Hospital 1989 - 91
Areawise attendance of patients from Maharashtra State *

	Konkan	Western Ghats	Khandesh	Marath-wada	Vidarbha	South M. S.	Total
Oesophagus	368 (52.6)	182 (48.0)	205 (45.8)	54 (56.8)	119 (55.6)	70 (47.6)	998 (50.0)
Stomach	96 (13.7)	62 (16.4)	58 (12.9)	9 (9.5)	21 (9.8)	22 (15.0)	268 (13.4)
Small Intestine	3 (0.4)	3 (0.8)	6 (1.3)	-	-	1 (0.7)	13 (0.6)
Colon	48 (6.9)	21 (5.5)	32 (7.1)	5 (5.3)	19 (8.9)	6 (4.1)	131 (6.6)
Rectosigmoid	5 (0.7)	6 (1.6)	1 (0.2)	2 (2.1)	1 (0.5)	1 (0.7)	16 (0.8)
Rectum	91 (13.0)	61 (16.1)	73 (16.3)	17 (17.9)	29 (13.6)	28 (19.0)	299 (15.0)
Anal Canal	17 (2.4)	9 (2.4)	25 (5.6)	2 (2.1)	5 (2.3)	6 (4.1)	64 (3.2)
Liver	24 (3.4)	18 (4.7)	25 (5.6)	3 (3.2)	8 (3.7)	6 (4.1)	84 (4.2)
Gall Bladder	6 (0.8)	2 (0.5)	2 (0.4)	1 (1.0)	-	2 (1.4)	13 (0.7)
Bile Duct	1 (0.1)	1 (0.3)	1 (0.2)	-	-	-	3 (0.2)
Ampula Vater	6 (0.8)	5 (1.3)	3 (0.7)	-	3 (1.4)	1 (0.7)	18 (0.9)
Pancreas	11 (1.6)	9 (2.4)	6 (1.3)	-	2 (0.9)	3 (2.0)	31 (1.6)
Retroperitoneum	23 (3.3)	12 (3.2)	11 (2.5)	2 (2.1)	7 (3.3)	1 (0.7)	56 (2.8)
Total	699	391	448	95	214	147	1994
All Cancer Cases	5390	3011	3325	678	1222	938	14564
Percentage of Oesophagus	6.8	6.0	6.2	8.0	9.7	7.5	6.8

** Reference : 1, 3 and 4 ; Figures in paranthesis show percentages*

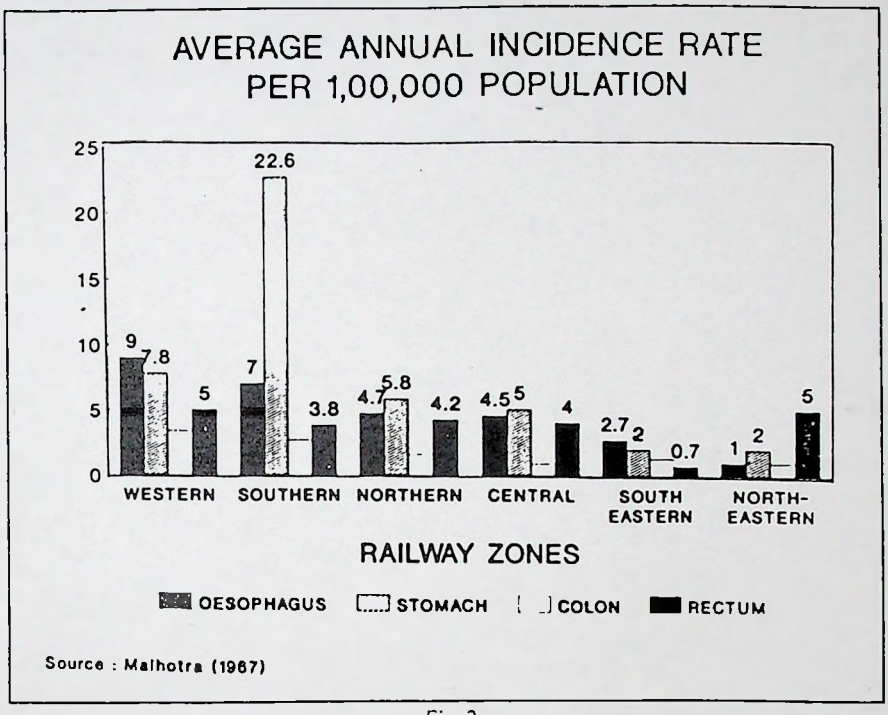

Fig. 2

in incidence between the Indian registries. The incidence rate in males varied from 11.4 per 100,000 in Pune to 7.6 in Madras and in females from 5.6 in Ahmedabad to 12.4 per 100,000 in Pune. Though rates in India are not as high as reported in Africa and some pockets in Iran, incidence rates are 2-3 times higher in males and five times higher in females than the rates in Connecticut Registry, (U.S.).

Global Incidence, mortality

Available incidence data from various parts of the world indicate that there is extreme diversity of rates. Incidence rates are estimated to be as high as 195.3 per 100,000 females and 165.5 for males in northern Gonbad in the Caspian region of Iran[10]. There seems to be high risk areas of the world which ranges from the Caspian Littoral in northern Iran through the southern republics of USSR[11] (Turkmenistan, Kazakhstan and Uzbekstan) to western and northern China. The other high risk areas includes part of eastern South America and certain areas of western Europe namely France and Switzerland.

The incidence rate and number of new cancer cases of 18 different cancers were estimated for the year 1985 in 24 areas of the world [12]. About 7.6 million (excluding non melanoma skin cancer) persons in the world developed cancer disease, and majority of them about 52%, were estimated to be in the developing countries. Oesophageal cancer

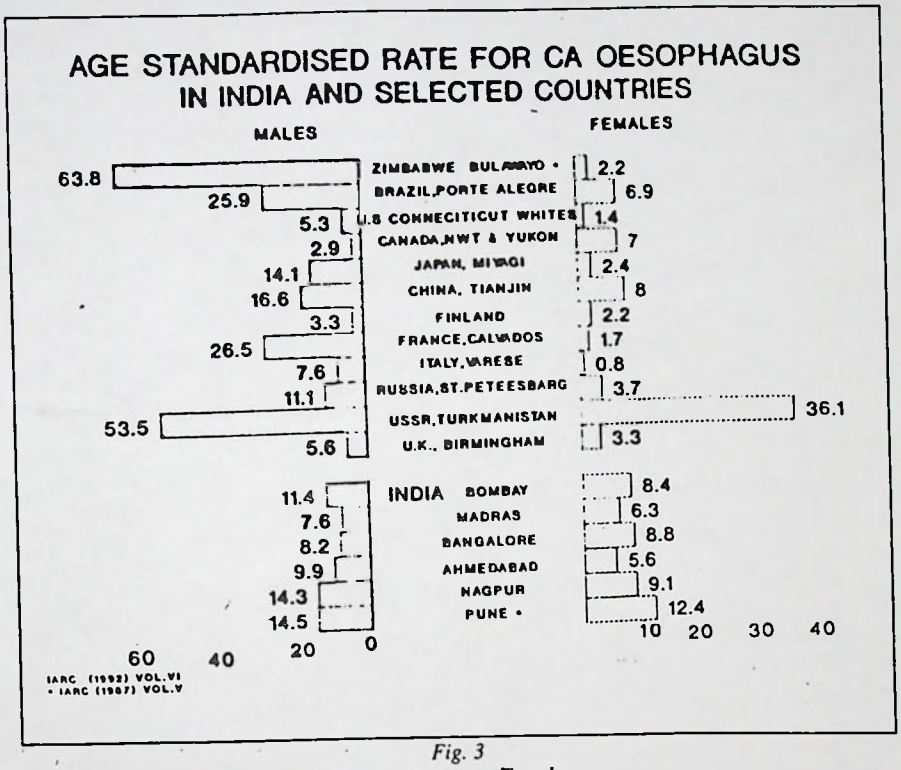

Fig. 3

was ranked 7th among males and 10th among females. Over 1,96,000 males and 1,08,000 females were estimated to be with this cancer. In the Southern Asia region which includes countries like India, Pakistan, Iran and Bangladesh, there were 32,000 males and 24,400 females with oesophageal cancer. The age adjusted rates in Southern Asia were 9.1 in males and 7.1 in females per 10^5 respectively. The mortality rates for oesophageal cancer in this area were estimated to be 8.9 per 10^5 in males and 6.7 per females [13]. The mortality rates, as high as 211.2 in males and 136.5 in females per 100,000 have been reported from Linxian county in China [14].

Trends

Available data from Bombay, India, indicate that the age adjusted incidence rate in males during 1964-72 was 13.7 per 10^5 and it decreased to 10.3 per 10^5 persons over a period of 25 years [15, 16, 17, 18]. The decreasing trend was almost similar in females. Jayant and Yeole (1987)[19] analysing the cummulative rates for various birth cohorts born between 1913 and 1943 did not find significant change in the rate over the years (Table IV). International trends based on mortality data suggest that the rates are declining in Nordic countries, Switzerland and Federal Republic of Germany and increasing in France, in US blacks and in Australia.

Religious Group

Epidemiological studies carried out in Bombay have highlighted the variation in incidence among major religious groups. Hindus, Muslims, Christians and Parsis are the major religious groups living in Bombay. Age adjusted incidence rates per 100,000 for Greater Bombay population by religion and sites are shown in Table III. Comparison of incidence rates for oesophagus and stomach cancer for both sexes show higher incidence of oesophageal cancer among Hindus (16.6), and Muslims (15.4) but not among Christians and Parsis where higher incidence of stomach cancer was observed. Parsis, followers of Zorastrian faith, generally do not indulge in tobacco habit as it is forbidden by religious customs. The low rates observed for oesophageal and stomach cancer among Parsis compared to other religious groups could be due to religious ban on tobacco habits. Further studies are required to confirm. Variation in incidence among ethnic groups has also been reported in the world. The incidence rates for oesophageal cancer in U.S. blacks are about four fold higher than those in U.S. whites and the rates in Singapore Chinese are higher than Singapore Indians and Singapore Malays [20].

Year 2000 A.D.

Based on the data from five metropolitan cancer registries it has been estimated that in 1992 there were around 6,44,600 cancer cases in India [7] of which about 40,000 persons were affected with oesophageal cancer. Based on 1992 estimates, it is estimated that there would be about 8,06,000 persons with cancer disease, of which 57,000 oesophageal cancer cases would be recorded in 2000 A.D. annually in India (Fig. 4).

Multiple Primaries

The appearance of second cancer

Table III

Trend of Esophageal Cancer in Greater Bombay 1964-90
Age Adjusted Incidence Rate per 100,000

Year of Diagnosis	Oesophagus		All Sites	
	Male	Female	Male	Female
1964-72	13.7	10.5	137.7	122.7
1973-78	12.7	10.4	126.5	123.6
1979-84	10.8	8.9	115.1	113.7
1985	11.6	8.9	129.5	122.9
1986	11.4	8.3	128.5	120.9
1987	11.8	8.8	130.4	118.8
1988	11.4	8.0	129.6	122.7
1989	11.5	8.2	130.4	120.4
1990	10.3	9.2	138.9	124.9

Reference : 15, 16, 17 and 18

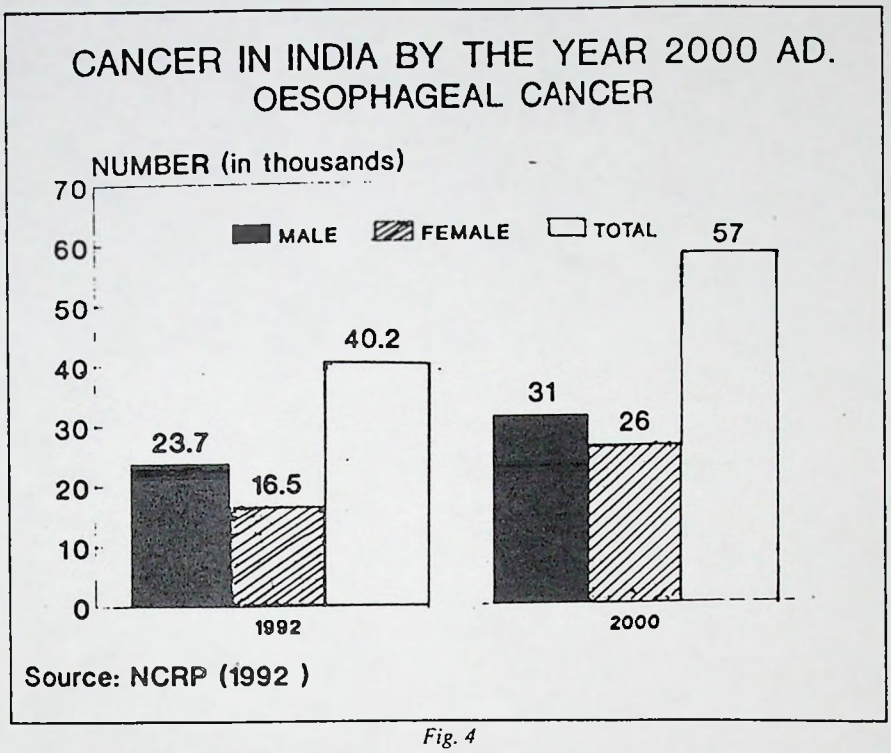

Fig. 4

among oesophageal cancer patients or second cancer in oesophagus after primary elsewhere has been reported in the literature. In a retrospective Indian study, Vyas et al (1983)[21] analysed 177 multiple primary cancers encountered at the Tata Memorial Hospital, Bombay during the period 1945-1981. The study reported that among 38 synchronus lesions, there was only one male patient with cancer in oesophagus and larynx diagnosed simultaneously. Among metachronus lesions, there were five patients with oesophageal cancer who developed second primary in the head and neck region and the site oesophagus as second primary was reported in 12 cases out of a total of 71 cases with the first lesion in head and neck region. The association of squamous cell carcinoma of head and neck with cancer of oesophagus observed in the study, has also been reported elsewhere [22].

Analytical Studies

Some of the known associated factors with cancer of the oesophagus such as tobacco use, alcohol consumption, dietary aspects based on the studies carried out in India and elsewhere are presented and discussed. Table V gives the summary of case-control studies conducted in India and the risk estimates for individual factors.

Tobacco Use

Pan, a preparation consisting of green betel leaf containing sliced betel nut, slaked lime and some spicy ingredients, is a

common form of chewing habit in India. Pan is chewed with or without tobacco.

'Bidi', an Indian cigarette, containing 0.2-0.3 gm of tobacco rolled in a dried leaf, usually temburni leaf (Diospyros melanoxylan) is commonly smoked in India. The different types of smoking in India are described in Sanghvi et al (1980) [23].

There are many other case-control studies conducted on oesophageal cancer in India where chewing and smoking have been implicated as the risk factors. The risk level varied from two-fold to 16-fold for chewers.

In one of the earliest studies, Sanghvi et al (1955) [24] found that bidi smoking was associated with the oesophageal cancer. The risk estimates were 2.9 for smokers only, 3.5 for chewers only and 5.3 for chewers and smokers.

In a historic case-control study of 3255 oesophageal cancer patients seen during the period 1963-71 and 5266 hospital controls, Paymaster et al (1937) [25] analysed the risk factors in particular chewing and smokig habits. The unique feature of this study was the assessment of risk factors in both sexes according to major segments of the oesophagus. The study also showed that the risk was higher in both males and females if tobacco was added to the chewing quid. Further the study showed increased risk due to bidi smoking either alone or with tobacco chewing (Fig. 5). In evaluating the risk according to segments of the oesophagus the study showed that chewing and smoking both were associated with all the segments of oesophagus in both the sexes. The smoking habit particularly enhanced the risk for cancer in upper third of oesophagus in both males and females (Fig. 6).

Studies by other workers confirmed the causal role of bidi smoking in oesophageal cancer. Jussawalla and Deshpande (1971) [26] estimated the relative risk for bidi smokers around 8-fold. Jayant et al (1977) [27] showed that chewing and

Table IV

Age adjusted incidence rate per 100,000 by major religious groups and sites for Greater Bombay 1973-78 *

	Major Religious Group							
	Hindu		Muslim		Christian		Parsi	
	Male	Female	Male	Female	Male	Female	Male	female
All Sites	150.9	135.6	161.3	145.0	147.0	128.9	106.7	129.5
Oesophagus	16.6	12.6	15.4	14.2	12.3	5.3	5.1	1.8
Stomach	9.4	6.1	9.1	6.6	16.3	9.1	5.5	5.5
Colon	3.3	3.4	2.7	3.9	3.4	4.1	7.7	4.0
Rectum etc.	4.5	2.7	4.5	3.9	4.9	1.8	3.3	3.6
Digestive	41.6	29.7	38.3	33.8	44.0	23.1	30.8	19.4

* *Reference : 16*

smoking acted synergistically in the development of oesophageal cancer.

A case-control study of 503 male oesophageal cancer cases and 634 controls carried out at the Tata Memorial Hospital gave estimates for chewers, smokers and alcohol drinkers by dietary practice namely vegetarian and nonvegetarian diet [28]. For the vegetarian group, none of the habit categories showed a significant association with oesophageal cancer. The study pointed that the dietary habit is also to be considered in evaluating the risk (Table VI).

In recent case-control study from Bangalore, South India, Ramesh (1993) [29] found a 2-fold excess risk for chewers and 6-fold excess risk for smokers. The risk enhanced to a level of 13.2 for those with dual habits (chewing and smoking). Bidi smoking in particular was a significant risk factor in this study. A dose-response relationship for bidi smoking and tobacco chewing by frequency and duration of habit was observed in this study. Also swallowing of quid juice and early age at starting of the habits were found to be contributory factors in the development of oesophageal cancer.

Studies conducted elsewhere have also demonstrated a dose-response relationship between quantity of tobacco smoked and increased risk of oesophageal cancer [30].

Doll (1971) [31], in his extensive review of both prospective and retrospective studies on oesophageal cancer stated "tobacco smoking to be causally associated with

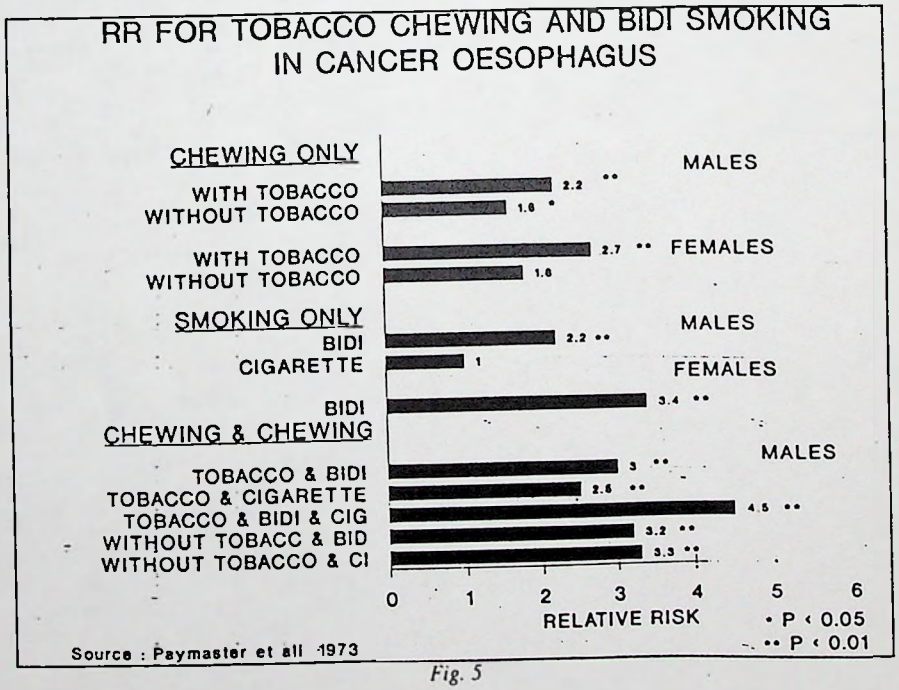

Fig. 5

Table V

Case-control studies on Oesophageal Cancer reported from India

Author & Year	Relative Risk			
	Chewing	Smoking	Chew+Smok	Alcohol
1. Sanghvi et al (1955) (M)	3.5	2.9	5.3	-
2. Paymaster et al (1968) (M)	1.9	2.5	3.1	-
(F)	2.5	2.4	3.6	-
3. Jussawalla & Deshpande (1971a)	2.5	2.9 (Bidi)	6.2	-
		1.0 (Cig.)	-	-
	3.5 (Non-tob.)	-	-	-
	2.1 (Tob.)	-	-	-
4. Paymaster et al (1973) (M)	2.1	1.9	2.8	-
(F)	2.4	2.8	1.6	-
5. Jayant et al (1977)	2.54	2.17	6.15	-
6. Jussawalla (1971b)	2.9 (Tob.)	8.0 (Bidi)	36.2	12.0 - 18.1
7. Jussawalla (1981)	2.8 (Tob.)	5.3 (Bidi)	-	-
	12.1 (Non-Tob.)	2.7 (Cig.)	-	-
8. Notani & Jayant (1987)	1.5 (NS)	3.2	3.3	-
9. Notani (1988)	1.6	4.0	6.3	12.2 - 47.9
10. Rao et al (1989)	1.3 (NS)	1.7	1.6	3.8 - 19.5
				2.4 (Smok.+Alch.)
11. Ramesh (1993)	2.6	6.4	13.2	11.4 - 18.0

NS - Statistically not significant *M - Males;* *F - Females*

oesophageal cancer consistently in all the studies".

Cigarettes with varying tar yields [32] and use of black tobacco in smoking [33] were found to enhance the risk for oesophageal cancer. In Caspian Littoral belt of Iran, Cook-Mozaffari et al (1979) [34] showed cigarette smoking to be a factor whereas there was no association between nass-chewing and oesophageal cancer.

Alcohol

Besides, tobacco use, alcohol consumption has been implicated as a risk factor in the development of oesophageal cancer. One of the earliest study by Wynder and Bross (1961) [35] showed that the proportion of alcohol drinkers were in excess in the oesophageal cancer group. In Europe, as well alcohol seems to be related to cancer of the oesophagus. Perhaps the choice of beverage, rather than amount of alcohol, is more important, for in Africa, beer brewed from maize seems to be associated with a higher incidence of oesophageal carcinoma than in beer brewed from other grains [36].

IARC (1988) [37] in a monograph on extensive review on evaluating the carcinogenic risk to humans from retrospective cohort studies of alcoholics and

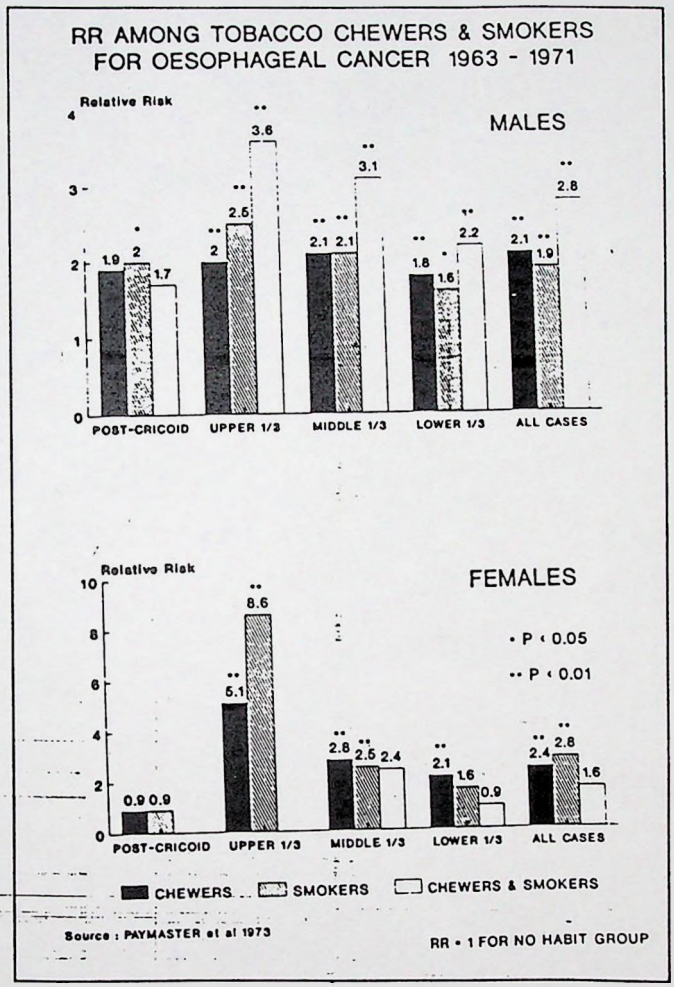

Fig. 6

brewery workers and case-control studies concluded that alcohol beverages were causally related to cancer of the oesophagus.

Notani (1988) [38], in a case-control study, from Bombay, showed that a 12-fold excess risk was found for men who had alcohol and tobacco chewing habit and 30-fold excess risk for those with smoking and alcohol habit. The risk for alcohol-chewers-smokers combined in that study was as high as 47.9 times for developing oesophageal cancer.

Rao et al (1989) [28] reported the

relative risk estimates for regular alcohol users with the duration of habit in years. Considering relative risk of alcohol users in 10 years as 1, relative risks for 11-20 years, 21-30 years and 30+ years are shown in Fig. 7. The risk increased with the increasing duration of habit.

'Samsu', a strong liquor, a form of spirit where alcohol content is equivalent to that of whisky, is consumed often by Chinese in Singapore. de Jong et al (1974) [39] in their study have shown that those who consumed 'samsu' had a 3-fold excess risk for oesophageal cancer. Similar excess risk for alcohol drinkers was observed in studies conducted elsewhere [29, 30, 41, 42, 43, 44].

Diet

Table VII gives some of the dietary items that have been identified as significant factors in the etiology of oesophageal cancer. The role of major items of daily diet in upper aerodigestive tract cancers was analysed by Notani and Jayant (1987) [45]. The study brought out increased use of red chilli powder in the diet as a significant risk factor for oesophageal cancer. Dose-response relationship of its usage was also shown, Intake of pulses, vegetables and fruit showed protective effect. Intake of flesh food (except fish) didn't show any positive effect on the risk of oesophageal cancer.

Intake of very spicy food was found

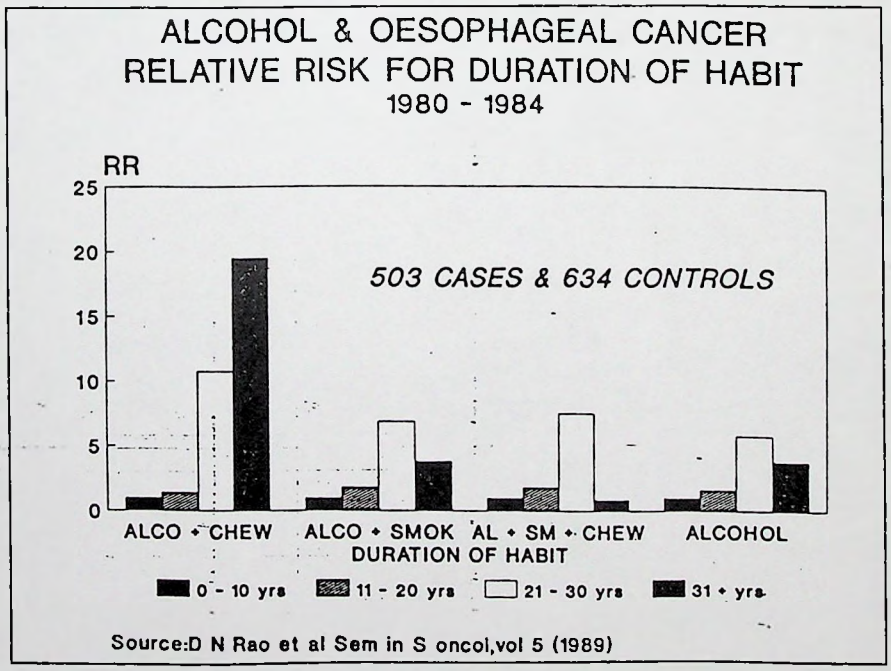

Fig. 7

to enhance the risk (2-fold) for oesophageal cancer compared to nil/moderate use of spices in food [29].

Recently consumption of salted tea in Kashmir has been shown to be a possible risk factor for oesophageal cancer [46].

Mate, a Uruguayan tea made from the herb Ilex paraguayensis is drunk very hot through a metal straw in large quantities. Individuals who drink more than 2.5 litres of mate daily have a 12-fold risk of developing oesophageal cancer. For those who drink lots of mate and also smoke heavily the risk is about 22-times [33].

Correlation studies by Joint Iran-IRAC (1977) [47] conducted in Caspian Littoral of Iran and Ziegler et al (1981) [48] found that low intake of pulses, fresh and citrus fruits, green vegetables, fish protein, low intake of dietary Vitamin A and Vitamin C were high risk factors for oesophageal cancer. Intake of animal proteins, in the form of fresh meat and fish, polyunsaturated fats, citrus fruits and oil intake were found to be protective dietary items for oesophageal cancer [49, 50]. Earlier, Segi (1975) [51] reported a direct association between mortality of oesophageal cancer and intake of tea-cooked rice gruel. Consumption of hot tea gruel and hot green tea[52] and drinking hot coffee[53] were found to increase the risk of developing oesophageal cancer.

Table VI

Relative risk (RR) estimates and confidence intervals for factors studied @

	Vegetarian	Non-vegetarian	Total
Chewers	1.07 (NS) (0.01, 88.9)	1.15 (NS) (0.9, 1.4)	1.32 (NS) (0.8, 2.1)
Smokers	1.2 (NS) (0.4, 3.7)	2.3 ** (1.3, 3.95)	1.7 **** (1.1, 2.7)
Chewers + Smokers	1.3 (NS) (0.4, 4.2)	1.8 (NS) (0.9, 3.5)	1.6 (NS) (0.95, 2.6)
Alcohol + Chewers	-	2.6 * (1.14, 5.9)	2.15 ** (1.03, 4.5)
Acohol + Smokers	-	3.1 **** (1.7, 5.4)	2.4 ** (1.5, 3.9)
Alcohol + Chewers + Smokers	3.6 (NS) (0.16, 78.6)	4.9 *** (2.07, 11.5)	3.8 *** (1.9, 7.9)

@ - Adjusted for 3 levels of age groups and 3 levels of area of residence

** - p < .05; ** - p < .01; *** - P < .001; **** - p < .025 ; - - only one control with this habit and not done; NS - not significant ; RR - is one for non-chewers, non-smokers and non-drinkers*

Figures in parentheses show lower and upper confidence limits

Due to small numbers alcohol alone not considered.

(Courtesy - Publishers)

Table VII

Some selected studies on dietary aspects and Oesophageal Cancer

Sr. No.	(Ref. No.)	Author, year of publication	Dietary Items	Remarks
1.	(45)	Notani and Jayant (1987)	Vegetables	Protective
			Fruits	Protective
			Fish	Protective
			Buttermilk	Protective
			Red chilli powder > 75 g/cu/month	Risk
			Tea drinking (> 2 cup/day)	Risk
2.	(28)	Rao et al (1989)	Vegetarian diet	Protective
3.	(47)	Joint Iran-IRAC (1977)	Fresh fruits	Protective
			Green Vegetables	Protective
			Fish Protein	Protective
4.	(49)	Tuyns et al (1987)	Animal Protein	Protective
			Polyunsaturated fats	Protective
			Citrus Fruits	Protective
			Oil Intake	Protective
5.	(54)	Li et al (1989)	Wheat, corn	Risk
6.	(55)	Cheng et al (1992)	Pickled vegetables	Risk
7.	(56) (57)	Van Rensberg et al (1985) Segal (1988)	Maize consumption	Risk
8.	(58)	Yu Y et al (1993)	Pork	Risk
			Corn	Risk
			Surface Water use	Risk
9.	(46)	Kumar et al (1992)	Salted Tea	? Risk
10.	(29)	Ramesh (1993)	Use of very Spicy food	Risk

The risk tended to increase with the increased intake of wheat and corn [54] and intake of pickled vegetable [55]. There has been reports of maize consumption in different forms and increased risk of oesophageal cancer [56,57].

A retrospective cohort-study of 12,693 individuals in Linxian, a high risk area in China was analysed to identify the dietary and potential risk factors [58]. They found that pork consumption, surface water use, corn as a primary staple food and

infrequent consumption of fresh vegetables were high risk factors for oesophageal cancer.

Other Risk Factors

Illiteracy [35, 39] and low socio economic groups [53] were found to be high risk groups for oesophageal cancer.

The influence of geo chemical elements on the risk of oesophageal cancer was analysed using the data on oesophageal mortality of 78 countries of Hubei province, China. High correlation was observed between some geochemical elements and oesophageal cancer. Four factors, metamorphic rock, zinc, copper, chromium were suspected factors which needed further study [59].

An excess risk of the order of ten was found in a follow up study of vulcanisation workers [60]. Workers involved in metal work [40] were high risk groups for oesophageal cancer.

Compared to other Swedish males, brewery workers have a significantly higher incidence of cancer of oesophagus, rectum, pancreas and lung [61].

Previous exposure to ionising radiation has also been implicated [62]. The long term stasis in untreated achalasia has also been recognised, although it is of interest that most of the tumours in the achalasia occur in the middle of the oesophagus instead of at the bottom, where presumably the stasis changes would be the most marked.

Chronic irritation of the oesophageal mucosa may be one of the predisposing factors leading to carcinoma. It has been estimated that the incidence in patients with lye strictures is much higher than in age and sex matched controls [63, 64]. Another rare disease in which cancer of the oesophagus is increased is tylosis, a genetically transmitted disease characterised by thickened skin of the hands and feet [65]. Other type of oesophageal injury may also lead to a high risk of cancer - Chaga's disease.

Oesophageal cancer is an important model for epidemiologic thinking. In the U.S. oesophageal cancer in Whites is caused primarily by a combination of cigarette smoking and high alcohol consumption although neither factor alone produces much, if any excess risk. In northern Sweden the primary cause is the dietary deficiency associated with the Plummer Vinson Syndrome and no carcinogen has been identified. Fortunately the incidence of Plummer Vinson Syndrome seems to be decreasing.

A careful epidemiological search in Iran where the high risk and low risk areas are only 300 miles apart showed no increase in exposure to aflatoxins, nitrosamines, alcohol or cigarettes. The only pronounced difference seemed to be bread consumption in the high risk zone and rice consumption in the low risk area [66, 67].

Another association with important clinical implication is that between carcinoma of the oesophagus and carcinoma of the head and neck [22]. Eighty nine of 850 patients with oesophageal carcinoma were found to have either synchronus or metachronus squamous cell head and neck tumours. This was nine times the expected rate. Both tumours were thought to be related to the use of tobacco.

Based on the reported studies, the following factors seemed to be involved in oesophageal carcinogenesis (1) direct alcohol and/or acetaldeyde mediated toxic effect on oesophagus epithelium (2) enhanced activation of pro-carcinogens by alcohol

induced enzymes dependent on cytochrome P-450(E) (3) nutritional deficencies, especially of zinc (4) Vitamin A and Riboflavin (5) changes in oesophageal mobility causing gastroesophageal reflex with injury (6) and altered salivary status [68, 69, 70, 71, 72, 73].

Conclusion

Epidemiological studies conducted in Indian and in other countries have clearly demonstrated the association of tobacco and alcohol habits with oesophageal cancer. It is time for the health planners and governments to take immediate action to prevent this cancer.

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Epidemiology of Esophageal Cancer

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The incidence of cancer of the oesophagus is high in India but not as high as the rates reported from the Caspian Littoral of Iran. Incidence data available for three places in India—Bombay, Madras, and Bangalore—show regional variations. In Bombay, the rates for males are high compared to Madras and Bangalore.

A case control study of 503 oesophageal cancer cases in males and 634 controls registered at the Tata Memorial Hospital during the period 1980–84 was carried out to determine the association of oesophageal cancer with two types of dietary practices, viz., vegetarian and non-vegetarian, in addition to tobacco and alcohol habits. In the presence of an alcohol habit, the relative risk for tobacco chewing and smoking was observed to be high in the non-vegetarian group compared to the vegetarian group. A vegetarian diet was protective. Further studies are suggested to confirm this finding.

KEY WORDS: oesophagus, alcohol, tobacco, diet

INTRODUCTION

Variations in the incidence of cancer of the oesophagus are noted not only between countries but also within a single country. The high rates reported from the Caspian Littoral of Iran are not uniformly the same even in different areas [1]. Case control studies conducted in different parts of the world indicate a high association of tobacco habits, alcohol consumption, and diet with cancer of the oesophagus [2,3]. Very few studies from India have identified the association of alcohol with oesophageal cancer. This is mainly due to lack of information on alcohol consumption. This study addresses itself to the association of diet, alcohol, and tobacco with oesophageal cancer.

MATERIALS AND METHODS

Three population-based registries in India provide incidence rates for the period 1982–85 [4–7] and the Bombay Cancer Registry provides incidence data for the period 1964–85.

Five hundred three males with oesophageal cancer were interviewed during the period 1980–84 and information on habits and customs were recorded in a special pro forma. During the same period 634 patients who attended the hospital but did not have any type of cancer or any infectious disease were also interviewed for their social habits and customs. The pro forma did not elucidate minor dietary practices but was restricted to the two major categories, viz., pure vegetarian and non-vegetarian diet. Hence, the analysis is restricted to the two categories only. Chewing, smoking, and alcohol habits were analysed according to diet habit. The study based on these materials is presented.

RESULTS

Hospital Data

Oesophageal cancer formed about 9% of all cases seen at the Tata Memorial Hospital. Among 255,077 cancer cases recorded during 1941–85, 23,742 (9%) cases were diagnosed as oesophageal cancer. The relative frequency was 8% among 16,154 total cancers seen in 1941–50, and in 1981–85 it was 7.2% among 53,641 total cancer cases seen during these years.

Among 1,612 cases, out of a total of 22,605 cases seen during 1984–85 the middle third was affected in 781 (48%) cases, lower third in 465 cases (29%), upper third

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TABLE I. Age-Adjusted (World Population) Incidence Rate (AAR) and Truncated Standardised Rate (TR) for Oesopha... in Three Population-Based Registries in India

	1982		1983		1984		19...
	AAR	TR	AAR	TR	AAR	TR	AAR
Males							
India							
Bangalore	9.3	17.1	7.1	12.1	8.4	18.9	6.6
Bombay	11.9	19.8	10.0	15.6	12.1	20.2	11.4
Madras	7.8	16.7	7.0	13.6	7.3	13.7	8.8
U.S.A.							
Connecticut (1973–77)	5.3	8.4					
France (Bas-rhin) (1975–77)	17.0	38.6					
Females							
India							
Bangalore	8.2	16.2	8.6	17.0	10.7	20.6	6.3
Bombay	9.1	13.8	7.9	15.1	8.4	16.1	8.9
Madras	3.6	8.7	6.2	12.2	5.9	11.9	6.0
United States							
Connecticut (1973–77)	1.7	3.3					
France (Bas-rhin) (1975–77)	0.8	1.4					

in 187 cases (12%), and more than one segment was involved in 179 cases (11%). The sex ratio (M:F) was 1.8:1.

Incidence

Table I shows the age-adjusted incidence rate of oesophageal cancer in three population-based registries for the period 1982–85. In both sexes, the rates observed in the Indian population are about thrice as high as that of United States (Connecticut) rates. The rate for males in Bombay is high compared to the rates for males in Bangalore and Madras for all the years, whereas there has been a variation amongst the females in the three population-based registries. The rates among females are not as high as the rates among males.

Case Control Study

The distribution of cases and controls according to habits (tobacco chewing, smoking, and alcohol consumption) and dietary practices are shown in Table II. Fourteen percent of cases and 28% of controls did not have such habits. Twenty-six percent of the cases consumed alcohol, whereas only 15% of the controls did. Alcohol consumption includes locally made "desi liquor" and/or foreign liquor. The habits of chewing "paan" and smoking are prevalent. "Paan" is made of betel leaf, areca nut, slaked lime, and catechew with or without tobacco and other ingredients. No attempt has been made to distinguish chewers of "paan" with or without tobacco. Smoking is mainly of a locally made cigarette, the "bidi," which consists of tobacco placed inside dry leaves of a tree of the ebony family. The "bidi" is 0.5 cm in length and contains an aver... 0.216 g of tobacco. Conventional cigarettes ... smoked. In this study, both bidi and cigarette ... are included as smokers of tobacco.

One hundred eighty-six cases (37%) and 150 co... (24%) belonged to the vegetarian group.

Among oesophageal cancer patients, 186 were ... dents of Bombay; 197 were from Maharashtra sta... cluding Bombay; and 120 were from other parts of I... Among controls 386 were from Bombay, 136 were ... Maharashtra state, and 113 were from other parts ... dia.

The relative risks (RR) for different habit groups ... estimated by odds ratio, by stratification over 9 str...

TABLE II. Distribution of Habits Among Oesophageal C... Cases and Unmatched Controls 1980–84

	No. (%)*		
Habits	Cases		Co...
No habits	70	(14)	175
Chewers	95	(19)	120
Smokers	119	(24)	129
Chewers + smokers	76	(15)	86
Alcohol + chewers	23	(5)	30
Alcohol + smokers	76	(15)	67
Alcohol + chewers + smokers	31	(6)	15
Alcohol alone	4		10
Food habits			
Vegetarian	186	(37)	150
Non-vegetarian	317	(63)	484
Mean age (yr)	55.0		45.8
Standard deviation	10.25		12.6

*Two controls and nine cases habit status not known.

LE III. Relative Risk Estimates and Confidence Intervals Factors Studied†

	Vegetarian	Non-vegetarian	Total
vers	1.07 [NS]	1.15 [NS]	1.32 [NS]
	(0.01, 88.9)	(0.9, 1.4)	(0.8, 2.1)
kers	1.2 [NS]	2.3**	1.7****
	(0.4, 3.7)	(1.3, 3.95)	(1.1, 2.7)
vers + smokers	1.3 [NS]	1.8 [NS]	1.6 [NS]
	(0.4, 4.2)	(0.9, 3.5)	(0.95, 2.6)
hol + chewers	—	2.6*	2.15**
		(1.14, 5.9)	(1.03, 4.5)
hol + smokers	—	3.1****	2.4**
		(1.7, 5.4)	(1.5, 3.9)
hol + chewers	3.6 [NS]	4.9***	3.8***
smokers	(0.16, 78.6)	(2.07, 11.5)	(1.9, 7.9)

usted for 3 levels of age groups and 3 levels of area of residence. $< .05$; $^{**}P < .01$; $^{***}P < .001$; $^{****}P < .025$; —, only one rol with this habit and not done; [NS], not significant. RR is one ba-chewers, non-smokers, and non-drinkers. Figures in paren- s shows lower and upper confidence limits.

age (40 years, 40–50, 50+) and 3 for area of resi- ce (Bombay, Maharashtra state excluding Bombay, of India). The 95% confidence intervals for the es- ates of RRs were computed using a test-based interval mation procedure. A chi-square test with 3 df for ciation for the duration of alcohol habit and a chi- are test with 1 df for trend were carried out [8,9]. he relative risk and confidence interval for various its are shown in Table III. For the vegetarian group, e of the habit categories showed a significant asso- ion with oesophageal cancer. In contrast to this, for non-vegetarian group only non-drinking smokers wed a significant association, with a relative risk of In the presence of alcohol habit both chewers and kers showed a significant association. The data in- e the possibility of protective effect of vegetarian the presence of a tobacco or alcohol habit.

elative risk estimates for regular alcohol users with ion of habit irrespective of duration of other habits own in Table IV. Considering relative risk of alco- sers in 10 years as 1, relative risks for 21–30 years 30+ years are shown. The relative risk increased increasing duration of the habit except for the group 30+ years. Alcohol with chewing habits shows an increasing trend in RR, but all three habits combined did not show a significant rise in the RR with increasing duration of alcohol habit. The reason for reductions in relative risk with duration of habit for 30+ years may be due to the small number of cases and controls in that category.

DISCUSSION

Available data indicate that cancer of the oesophagus is high in India but not as high as reported in some other parts of the world [1,10]. Compared to Madras and Bangalore, the rates in Bombay are high in males but not so distinctly in famales. A variation in incidence rate among the religious communities in Bombay has been reported. The incidence rates among Hindus and Muslims were high compared to the rates in Christians and Parsis [11].

In this study there are certain limitations. Only males between ages 30 and 75 years were included. Hospital controls were used instead of population controls. Cases and controls were interviewed immediately after registration but before any medical examinations. All eligible cancer cases seen during the period 1980–84 could not be interviewed for many reasons. The findings of this study are therefore to be interpreted with caution.

Due to a government prohibition policy and the social stigma attached to alcohol drinking, information on alcohol habits in India is very difficult to obtain. The association of alcohol with cancer of the oesophagus has already been reported [2,3]. In our study this association was further supported.

The information on consumption of alcohol in terms of quantity per day was not available. Hence, duration in years for alcohol habit has been studied for trend. Due to the small number of cases and controls in the vegetarian group the RR with duration for alcohol usage could not be studied separately for vegetarian and non-vegetarian groups.

Several case control studies showed an association of dietary factors of possible significance in cancer of the oesophagus. At the same time some dietary items in the food played a protective role against cancer of the oe-

LE IV. Relative Risk Estimates for Regular Alcohol Users With Duration of Habit

	Years					
egetarian + vegetarian group)[a]	0–10	11–20	21–30	30+	*P*-value for association	*P*-value for trend
hol + chewers	1	1.4	10.8	19.5	<0.01	<0.001
hol + smokers	1	1.8	6.9	3.8	<0.01	<0.01
hol + smokers + chewers[b]	1	1.8	7.5	0.83	>0.25	>0.50
hol group[c]	1	1.6	5.8	3.8	<0.001	<0.001

lcohol with any other habit, duration of alcohol habit is considered.
gnificant.
es chewers and smokers.

sophagus [12,13]. Excessive tea drinking and use of red chili powder in the diet were shown to be high risk factors for oesophageal cancer [14]. In a prospective cohort study carried out in Japan, it was shown that the combination of daily smoking and drinking was a major risk factor, whereas the common use of green and yellow vegetables in the diet in the presence of the habit decreased the risk of oesophagus cancer [13].

Our study indicates the protective role played by a vegetarian diet in cancer of the oesophagus. More studies are warranted to confirm this finding.

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RISK ASSESSMENT OF TOBACCO, ALCOHOL AND DIET IN ORAL CANCER—A CASE-CONTROL STUDY

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A retrospective case-control study of 713 male oral-cancer patients seen at Tata Memorial Hospital, Bombay, during 1980–1984 was undertaken to assess the association between chewing, smoking and alcohol habits. Male controls were chosen among those persons who attended the hospital during the same period and were diagnosed as free from cancer, benign tumour and infectious disease. Statistical analysis was based on unconditional logistic regression and the confidence interval for RR was calculated using the standard error of the estimates. Established factors such as tobacco chewing and bidi smoking showed a significant association with oral cancer. For the alcohol habit, the relative risk was 1.42 and the dose-response relationship, in terms of frequency and duration of the habit, was also observed. The illiterate group showed an almost 2-fold significant excess risk compared to the literate group. After adjusting for confounding variables such as age, residence, illiteracy and known factors such as tobacco chewing and bidi smoking, the study has brought out the significance of a non-vegetarian diet as a high-risk factor for oral cancer compared to a vegetarian diet. Further studies are required to identify specific items in the non-vegetarian diet which may be associated with oral cancer.

In India, the association of tobacco chewing and smoking with oral cancer has been documented in earlier studies (Sanghvi *et al.*, 1955; Wahi *et al.*, 1965; Jussawalla and Deshparde, 1971; Jayant *et al.*, 1977; Notani, 1988; Shanta and Krishnamurthi, 1959; Sankaranarayanan *et al.*, 1989, 1990; Nandakumar *et al.*, 1990). The dose-response relationship of tobacco chewing and bidi smoking with oral cancer has also been demonstrated, not only for oral cancer as a whole but also for specific sites of oral cancer (Sankaranarayanan *et al.*, 1989, 1990). Many studies conducted elsewhere have reported a significant association of cigarette smoking and alcohol drinking with oral cancer (Rothman and Keller, 1972) (Wynder *et al.*, 1957). In India, there are conflicting reports concerning the association of alcohol with oral cancer (Notani, 1988; Nandakumar *et al.*, 1990). The purpose of the present study is to explore in detail the effect of alcohol in oral cancer and also to confirm the earlier findings on tobacco chewing and bidi smoking in oral cancer. In this country, with its vast ethnic and geographical variations and a wide variety of habits and customs, there exists a section of the population which adheres strictly to a vegetarian diet. An attempt has been made to evaluate the association of diet and the alcohol habit and its role in oral cancer.

MATERIAL AND METHODS

Oral cancer includes cancers of lip, anterior two-thirds of tongue, upper and lower alveolus, floor of mouth, buccal mucosa and hard palate. In our study, cancers of the base of the tongue (ICD 1410) and soft palate (ICD 1453) are not included in the oral cancer category.

Patients attending the hospital were interviewed by 2 trained social investigators before being clinically examined in the out-patient department. The questionnaire contained data items on demographic factors, family history of cancer, tobacco habits, use of alcohol, frequency, duration, cessation of these habits and dietary practices. Medical records were subsequently scrutinized for diagnosis and entered in the forms. Patients who were diagnosed as cancer-free were considered as "controls". During the period 1980–1984, 713 male patients with histologically confirmed oral cancer were interviewed, while 635 controls (unmatched) were chosen from among those controls who were diagnosed as being free from cancer, infectious diseases and benign lesions. Data on females were also collected but not included in this study because they were incomplete with regard to habits and customs. In general, chewers take *pan*, betel nut, lime and tobacco with some spices and condiments and smokers smoke Indian cigarette called bidis (obtained by wrapping 0.2g to 0.3g of tobacco in tendu leaf), cigarette, chutta (a kind of cigar), hukka and chilum (clay pipe). Bidi smoking and cigarette smoking are the commonest smoking habits. Alcohol is locally brewed liquour, mostly from palm trees (ethanol content 40%–60%). No distinction has been made between types of alcohol, and it is generally classified as being of local or foreign make. Collection of data items on diet was started in 1988 and hence, in this study, diets are broadly classified as vegetarian or non-vegetarian. Vegetarians, in general, do not consume poultry or fish products and avoid animal meat totally. Statistical analysis was based on unconditional logistic regression and 95% confidence limits for the estimated odds ratio were obtained from the standard errors of the estimate (Kleinbaum *et al.*, 1982) (Mantel and Haenszel, 1959).

RESULTS

Table I shows general characteristics of oral cancer patients and controls. The average ages for cases and controls are 50.35 yrs and 45 years, respectively. Distribution of cases and controls according to religion did not differ and hence was not adjusted in the later analysis. The cancer patients reported a high illiteracy rate compared to controls (47.9% *vs.* 28.8%). Sixty-eight (9.5%) patients and 175 (27.7%) controls did not have any of the habits considered in this study, while 645 (90.5%) oral cancer patients had at least one of the habits compared to 460 (72.3%) controls.

Tobacco chewing was more frequent in cases (64.3%) than in controls (39.5%). In all, 55 patients (7.7%) and 99 (15.6%) controls were cigarette smokers whereas 297 (41.7%) cases and 187 (29.4%) controls were bidi smokers. Alcohol alone as a habit was reported in 6 cases and 10 controls, and alcohol addicts also had at least one of the other habits, either tobacco chewing or smoking. The use of snuff, generally prevalent in this country, was rarely reported by either cases or controls, despite attempts to collect this information. Snuff was, therefore, excluded from the analysis.

Relative frequencies for cases and controls and RR estimates for chewing, smoking and the alcohol habit, along with tests of significance, are shown in Table II. For these 3 habits, the RR was significantly higher than one and when categorized further, bidi smoking and tobacco chewing emerged as significant risk factors for oral cancer.

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Frequency per day of tobacco chewing, bidi smoking and alcohol drinking along with RR estimates and tests of significance are shown in Table III. Tobacco chewing, bidi smoking and alcohol drinking showed increasing risk with increasing frequency and the trend was significant. The relative risk associated with chewing tobacco 21–30 times per day was 10.67 times higher than for non-chewers. Bidi smoking showed a significant increase in risk only for the frequency categories of 1–10 and 11–20 times per day.

RR estimates and tests of significance for tobacco chewing, bidi smoking and alcohol drinking according to duration of habit are shown in Table IV. The trend for dose-response relationship was statistically significant for all 3 habits. The risk level increased with the increase in duration of habits.

Food habit and educational status for cases and controls and their estimated RR are shown in Table V. The estimates were obtained after adjusting for 4 age groups (< 35, 35–44, 45–54 and 55 yrs+) and 3 areas of residence (Bombay, Maharashtra and "other"). Non-vegetarian diet and illiteracy emerged as high risk factors for oral cancer.

Unconditional logistic regression with multiplicative risk type was used to fit the model to the data. The factors considered were non-vegetarian diet, tobacco chewing, bidi smoking, alcohol habit and educational status after adjusting for age and residence. The model was fitted with stepwise addition of factors and the results are presented in Table VI. The non-vegetarian diet showed an 68% excess risk for oral cancer compared to the vegetarian diet with C.I. 1.26–2.24. The risk level for the non-vegetarian diet remained significant even after adjusting for factors such as tobacco chewing, alcohol and bidi smoking. Alcohol addiction carried a 50% significant excess risk for oral cancer after adjusting for other factors.

Information on cessation of the habit—in particular for tobacco chewing and bidi smoking—was analysed for both cases and controls. There were 168 cases and 41 controls who reported cessation of the tobacco habit, with a mean duration in years of 2.23 ± 4.01 and 3.22 ± 3.9, respectively, while 63 cases and 28 controls reported stopping bidi smoking, with a mean duration in years of 2.55 ± 4.13 and 2.39 ± 2.74, respectively. RR estimates for ex-tobacco-chewers and ex-bidi-smokers and test of significance are shown in Table VII. The relative risk for tobacco chewers did not show a reduction in risk for ex-chewers, whereas for bidi smoking there was a substantial reduction in the relative risk for those smokers who had stopped more than 2 years previously.

TABLE I – GENERAL CHARACTERISTICS OF CANCER PATIENTS AND CONTROLS, 1980–1984

	Cases	(%)	Controls	(%)
1 Total number	713		635	
2 Site				
Lip	30	4.2	—	
Ant. tongue	142	19.9	—	
Alveolus	123	17.3	—	
Floor of mouth	46	6.5	—	
Buccal mucosa	315	44.2	—	
Hard palate	23	3.2	—	
Tongue NOS	34	4.7	—	
3 Age group				
< 35 yrs	43	6.0	139	21.9
35–44 yrs	155	21.7	175	27.5
45–54 yrs	227	31.8	156	24.6
55+ yrs	288	40.3	165	26.0
Average age ± SD	50.35 ± 10.7		45.4 ± 12.9	
4 Residence				
Bombay	238	33.4	386	60.8
Maharashtra	233	32.7	136	21.3
Other	238	33.2	111	17.5
Not recorded	4	0.7	2	0.4
5 Religion				
Hindu Maharashtrian	297	41.7	255	40.2
Hindu Gujarati	55	7.7	59	9.3
Sindhi	8	1.1	15	2.4
Hindu, others	197	27.6	150	23.6
Muslims	109	15.3	104	16.4
Christians	22	3.1	28	4.4
Other religions	25	3.5	24	3.7

DISCUSSION

This is a retrospective case-control study. Cases and controls were interviewed in an out-patient department using the same

TABLE II – RELATIVE FREQUENCIES OF CASES AND CONTROLS AND RR ESTIMATES FOR CHEWING, SMOKING AND ALCOHOL HABITS, WITH TESTS OF SIGNIFICANCE

Type of habit	Cases	Controls	R.R.	95% C.I.[1] (lower-upper)	p-value
Chewing					
Non-chewers	251	385	1.0		
Chewers	462	250	2.83	2.26–3.56	<0.001
Chewing type					
Non-chewer	251	385	1.0		
Chewing with tobacco	450	234	2.95	2.34–3.71	<0.001
Chewing without tobacco	5	11	0.70	0.21–2.20	0.507
Chewing betel nut alone	7	5	2.15	0.60–7.88	0.186
Smoking					
Non-smoker	337	338	1.0		
Smokers	376	297	1.26	1.01–1.56	0.037
Smoking type					
Non-smokers	337	338	1.0		
Bidi	297	187	1.59	1.25–2.03	<0.001
Cigarette	55	99	0.56	0.38–0.81	<0.001
Bidi + cigarette	7	7	1.0	0.31–3.21	0.996
Others (hukka, chilum)	15	3	5.01	1.35–21.99	0.005
Not recorded	2	1			
Alcohol drinking					
No alcohol	531	511	1.0		
Alcohol	182	124	1.42	1.09–1.86	0.008

[1]Confidence interval.

TABLE III - RELATIVE FREQUENCIES OF CASES AND CONTROLS AND RR ESTIMATES WITH TESTS OF SIGNIFICANCE FOR CHEWING, SMOKING AND ALCOHOL BY FREQUENCY OF HABIT

Frequency of habit (per day)	Cases	Controls	R.R.	95% C.I.[1] (lower-upper)	*p*-value	Trend *p*-value
Tobacco chewing						
Non-tobacco-user	263	401	1.0			
1–10 times	373	203	2.80	2.21–3.55	< 0.001	
11–20 times	67	29	3.52	2.12–5.75	< 0.001	
21–30 times	7	1	10.67	1.32–232.3	0.006	
31 + times	3	1	4.57	0.42–114.7	0.150	< 0.001
Bidi smoking						
No H/o bidi smoking[2]	407	440	1.0			
1–10 times	163	95	1.85	1.38–2.50	< .001	
11–20 times	64	41	1.69	1.09–2.61	0.013	
21–30 times	66	52	1.37	0.91–2.06	0.109	
31 + times	10	6	1.80	0.60–5.62	0.252	
Not recorded	3	1				< 0.001
Alcohol drinking						
No alcohol habit	531	511	1.0			
Once	136	109	1.20	0.90–1.60	0.200	
Twice	46	15	2.95	1.58–5.60	< 0.001	< 0.001

[1]Confidence interval.–[2]H/o, history of.

TABLE IV - RELATIVE FREQUENCIES OF CASES AND CONTROLS AND RR ESTIMATES, WITH TESTS OF SIGNIFICANCE FOR CHEWING, SMOKING AND ALCOHOL BY DURATION OF HABIT

Duration of habit (in years)	Cases	Controls	R.R.	95% C.I.[1] (lower-upper)	*p*-value	Trend *p*-value
Tobacco chewing						
Non-tobacco-user	263	401	1.0			
1–10 yrs	79	94	1.28	0.90–1.82	0.149	
11–20 yrs	131	51	3.92	2.70–5.70	< 0.001	
21–30 yrs	137	48	4.35	2.38–6.37	< 0.001	
31 + yrs	103	41	3.83	2.54–5.79	< 0.001	< 0.001
Bidi smoking						
No H/o bidi smoking[2]	407	440	1.0			
1–10 yrs	61	64	1.03	0.70–1.53	0.876	
11–20 yrs	61	48	1.37	0.90–2.09	0.120	
21–30 yrs	86	39	2.38	1.57–3.64	< 0.001	
31 + yrs	96	43	2.41	1.62–3.61	< 0.001	
Not recorded	2	1				< 0.001
Alcohol drinking						
No alcohol habit	531	511	1.0			
1–10 yrs	53	63	0.81	0.54–1.21	0.282	
11–20 yrs	67	35	1.84	1.18–2.89	0.005	
21–30 yrs	46	14	3.16	1.66–6.11	< 0.001	
31 + yrs	13	11	1.14	0.47–2.75	0.756	
Not recorded	3	1				< 0.001

[1]Confidence interval.–[2]H/o, history of.

questionnaire, before the medical diagnosis was known to social investigators. This has largely eliminated interviewer bias in the collection of data. Only histologically confirmed oral cancer cases were included in this study. Not all of the oral cancer patients diagnosed during the period could be interviewed, for many reasons. Controls were chosen from among the interviewed patients who were diagnosed as being free from cancer, infectious diseases and benign neoplasms. The use of hospital controls instead of population controls may have affected the estimates of risk factors.

An attempt has been made to study the role of alcohol and diet in oral cancer. Diets are broadly classified as vegetarian and non-vegetarian. The major difference in diet between the groups is that vegetarians do not consume animal meat, fish and poultry products. Non-vegetarian food items are not commonly consumed on a daily basis in our population mainly for economic reasons. These are some of the limitations and hence the inferences drawn from this study need to be interpreted with caution.

The association of dietary components with oral cancer has already been reported (Nandakumar *et al.*, 1990) (Notani and Sanghvi, 1976; Notani and Jayant, 1987; Notani, 1988). It has been shown that the risk level for oral cancer decreased with the increasing use of dairy produce, fruit and vegetables but increased with increasing use of red chillies in the diet and cereal ragi as a main staple diet (Nandakumar *et al.*, 1990) (Notani and Sanghvi, 1976; Notani and Jayant, 1987). In our study, the non-vegetarian diet showed a 39% excess risk compared to the vegetarian diet after adjusting for known risk factors such as tobacco chewing, bidi smoking and alcohol, and confounding variables such as age, residence and educational status. In an international ecological study of nutrient predictors for oral and oesophageal cancer, the risk level has been shown to increase with increasing meat and animal fat consumption and to decrease with fruit and cabbage consumption (Hebert *et al.*, 1993).

Alcohol has been established as a factor in oral cancer in studies conducted elsewhere (Rothman and Keller, 1972; Wynder *et al.*, 1957). In our study the dose-response relationship also showed an increase in risk level with the increase in duration and frequency of the alcohol habit. Mantel-Haenszel

TABLE V – RR ESTIMATES AND TEST OF SIGNIFICANCE FOR EDUCATIONAL STATUS AND DIETARY HABITS AFTER ADJUSTING FOR AGE AND RESIDENCE

Factors	Cases	Controls	RR	95% CI[1] (lower upper)	*p*-value
Dietary habits					
Vegetarian	138	148	1.0		
Non-vegetarian	567	484	1.83	1.35–2.5	< 0.001
Not recorded	8	3			
Educational status					
Literate	362	450	1.0		
Illiterate	340	183	1.97	1.54–2.55	< 0.001
Not recorded	11	2			

[1]Confidence interval

TABLE VI – RR ESTIMATES AND TEST OF SIGNIFICANCE FOR NON-VEGETARIAN DIET, TOBACCO CHEWING, ALCOHOL USE AND EDUCATIONAL STATUS IN A STEPWISE MODEL

Factor	RR[1]	CI[2]	*p*-Value
1 Diet (0—Veg., 1—Non-veg.)	1.69	1.26–2.24	< .001
2 Diet (0—Veg., 1—Non-veg.)	1.68	1.25–2.25	< .001
Tobacco chewing (0—Nil, 1—Yes)	2.66	2.10–3.37	< .001
3 Diet (0—Veg., 1—Non-veg.)	1.49	1.09–2.01	0.010
Tobacco chewing (0—Nil, 1—Yes)	2.71	2.13–3.43	< .001
Alcohol (0—Nil, 1—Yes)	1.65	1.22–2.22	0.001
4 Diet (0—Veg., 1—Non-veg.)	1.38	1.01–1.87	0.041
Tobacco chewing (0—Nil, 1—Yes)	2.55	2.00–3.24	< .001
Alcohol (0—Nil, 1—Yes)	1.60	1.19–2.16	0.002
Education (0—Literate, 1—Illiterate)	1.77	1.38–2.28	< .001
5 Diet (0—Veg., 1—Non-veg.)	1.39	1.02–1.89	0.036
Tobacco chewing (0—Nil, 1—Yes)	2.64	2.07–3.38	< .001
Alcohol (0—Nil, 1—Yes)	1.51	1.12–2.05	0.007
Education (0—Lit., 1—Illit.)	1.69	1.31–2.18	< .001
Bidi (0—Nil, 1—Yes)	1.37	1.06–1.77	0.017

[1]Adjusted for age and residence (Bombay—1, Non Bombay—0).–[2]C.I.—Confidence Interval

RR estimates, after adjusting for 4 age groups and 3 areas of residence, were 3.6 for chewing only, 1.7 for smoking, 2.9 for the combined effect of chewing and smoking, 4.3 for chewing and alcohol, 2.4 for smoking and alcohol and 8.8 for all 3 habits (Table VIII). Addition of alcohol to the other habits increased the risk for oral cancer. In a recent study in India, it was reported that estimated relative risks for male oral cancer were 4.7 for smoking, 2.8 for chewing, 13.1 for smoking and chewing, 10 for alcohol and chewing, 17.0 for alcohol and smoking, and 47.1 for alcohol, chewing and smoking in a specific Hindu community (Notani, 1988).

Case-control studies on oral cancer carried out in different parts of India have established unequivocally the association with tobacco-chewing habits (Jussawalla and Deshpande, 1971; Sanghvi *et al.*, 1955; Wahi *et al.*, 1965). The present study has also brought out the significance of tobacco-chewing habits in oral cancer. The dose-response relationship in terms of frequency per day and duration in years, as reported in earlier studies, has also been confirmed in this study.

The smoking habit, in particular bidi smoking was associated with a significant excess risk of oral cancer, whereas cigarette smoking did not emerge as a high-risk factor. Previous studies in India also failed to establish the association between cigarette smoking and oral cancer (Jussawalla and Deshpande, 1971; Sankaranarayanan *et al.*, 1990), though a slightly elevated risk has been reported (Nandakumar *et al.*, 1990).

The comparison of risk level, as estimated in our study, with those reported from other studies in India requires careful evaluation. Account has to be taken of differences between studies in the composition of oral cancer categories and also of the inclusion or exclusion of females. It is well known that the habit patterns among males and females differ significantly. Due to the policy of prohibition adopted by many States in India, people do not generally admit to the habit of drinking and in particular females will never openly admit to this habit.

Literacy as a factor in oral cancer needs careful interpretation. Factors such as poor socio-economic status, undernourishment, tobacco habits and poor dental hygiene are

TABLE VII - MANTEL-HAENSZEL RR ESTIMATES AND TEST OF SIGNIFICANCE FOR EX-CHEWERS AND EX-SMOKERS

Factors	Cases	Controls	RR[1]	95% CI[2] (lower-upper)	*p*-value
Tobacco chewing					
Non-chewer	263	339	1.0		
Current chewer	279	193	2.21	1.71–2.92	< 0.001
Ex-chewer 1 yr	124	26	5.82	3.64–10.21	< 0.001
> 1 yr	42	15	2.57	1.42–5.77	< 0.001
Not recorded	5	2			
Bidi					
Non-smoker	414	447	1.0		
Current smoker	231	159	1.35	1.04–1.78	0.020
Ex-smoker 1 yr	42	14	2.07	1.06–4.31	0.023
2 yrs	10	3	2.19	0.52–11.97	0.225
> 2 yrs	11	10	0.67	0.23–1.92	0.402
Not recorded	5	2			

[1]Stratified by 4 age groups (< 35, 35–44, 45–54 and 55 yrs +) and 3 areas of residence (Bombay, Maharashtra, others).–[2] Confidence interval.

TABLE VIII - RR ESTIMATES AND TESTS OF SIGNIFICANCE FOR HABITS AFTER STRATIFICATION BY AGE GROUP AND RESIDENCE

Factors	Cases	Controls	RR	95% CI[1] (Lower-Upper)	*p*-value
No habit	68	174	1.0		
Chewer	215	120	3.64	2.51–5.67	<0.001
Smoker	106	128	1.69	1.10–2.68	0.013
Chewer + smoker	138	86	2.93	1.88–4.82	< 0.001
Alcohol	6	10	1.32	0.39–5.08	0.550
Chewer + alcohol	44	30	4.32	2.33–9.40	< 0.001
Smoker + alcohol	70	67	2.44	1.48–4.18	< 0.001
Alcohol + chewer + smoker	57	15	8.88	4.69–23.06	< 0.001
Others	4	3	1.98	0.34–14.19	0.370
Not recorded	5	2			

[1]Confidence interval.

commonly associated with illiteracy. Further studies are required to substantiate this finding.

Studies conducted in both high- and low-risk areas have clearly revealed the association of the tobacco and alcohol habits with oral cancer. It is necessary for government and health planners to take serious steps, in the light of these findings, with a view to preventing oral cancer.

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RISK ASSESSMENT OF TOBACCO, ALCOHOL AND DIET IN CANCERS OF BASE TONGUE AND ORAL TONGUE - A CASE CONTROL STUDY

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SUMMARY

This is a retrospective case-control study of male tongue cancer patients seen at Tata memorial Hospital, Bombay, during the years 1980-84. The purpose of the study was to identify the association of tobacco, alcohol, diet and literacy status with respect to cancers of two sub sites of tongue namely anterior portion of the tongue (AT) (ICD 1411-1414) and base of the tongue (BT) (ICD 1410). There were 142 male AT patients and 495 BT patients interviewed during the period. 635 interviewed male patients who were free of any disease were considered as control. Bidi smoking was found to be a significant risk factor for BT patients and tobacco chewing for AT patients respectively. Alcohol drinkers showed about 45% to 79% excess risk for both sites of tongue cancer. Illiteracy and non vegetarian diet proved to be a significant factor for AT patients only. The study brings out that the location of cancer has got a direct bearing with the type of tobacco use and other related habits and this inturn may provide meaningful interpretation of variations observed in the incidence of tongue cancer around the world.

INTRODUCTION

Tongue cancer is generally an uncommon disease and its reported incidence is below 5 per 100,000 in about 135 populations / countries around the world[1]. In India, among 5 metropolitan registries the incidence rate of tongue cancer (ICD 141) in males varied between 4.7/100,000 in Bangalore and 13.2/ 100,000 in Bhopal[2] Clinical description, behaviour and management of tongue cancer depend on the location of the lesion, either in the base or in the oral tongue Tobacco chewing, smoking and alcohol habit were established risk factors for oral and pharyngeal cancer (ICD 140 -149) in general[3,4,5,6,7,8,9]. The purpose of the study is to identify the risk of these established factors with respect to two sites of tongue, namely base of the tongue (ICD 1410) and oral tongue (ICD 141-144) and its risk with respect to type of tabacco use.

PATIENTS AND METHOD

This is a part of the retrospective unmatched case-control study of head and neck cancer patients who attended the hospital during the period 1980-84. There were 713 male oral cancer patients and 1498 male laryngo pharyngeal cancer patients who were interviewed by two social investigators at the time of registration in the Out Patient Department. The patients were interviewed before clinical examination and thus investigators were not aware of the diagnosis of patients. Among them, 142 patients had cancer in anterior portion of the tongue and 495 patients had cancer in base of the tongue. During the period, there were 635 interviwed male patients who were diagnosed as being free from cancer, infections disease and benign lesion and these patients were classified as hospital control. Majority of the male controls

Table I
General features of patients and controls

	Controls	(%)	Ant. Tongue (AT)	(%)	Base Tongue (BT)	(%)
1. Number	635		142		495	
Avg. Age+ S. D.	45.5 ± 12.9		49.1 ± 10.9		54.76 ± 9.7	
Range	25 - 87		27 - 75		29 -80	
2. Residence						
Bombay	386	60.8	56	39.4	186	37.6
Maharashtra	136	21.4	47	33.1	163	32.9
Others	111	17.5	38	26.8	146	29.5
Unkoown	2	0.3	1	0.7	-	
3. Religion						
Hindu Maharashtra	255	40.2	62	43.6	168	33.9
Hindu Gujarath	59	9.3	12	8.5	88	17.8
Sindhi	15	2.4	1	0.7	9	1.8
Hindu Others	150	23.6	39	27.5	119	24.0
Muslim	104	16.4	19	13.3	82	16.6
Christian	28	4.4	3	2.1	16	3.2
Other Religions	24	3.7	6	4.3	13	2.6
4. Habits						
No	175	27.6	23	16.2	36	7.3
Yes	460	72.4	119	83.8	459	92.7
5. Type						
Chewers	251	39.4	76	54.2	172	34.7
Smokers	295	46.8	69	49.3	404	81.6
Alcohol	122	19.4	39	28.2	113	22.8

whom we had considered for the study attended the hospital for complaints in head & neck region and later diagnosed to be of no evidence of disease or any abnormality. In general, chewers take pan, betal nut, lime and tobacco with some spices and condiments and smokers smoke Indian cigarette called bidis (obtained by wrapping 0.2g to 0.3g of tobacco in tendu leaf), cigarette, chutta (a kind of cigar) hukka and chilum (clay pipe). Bidi smoking and cigarette smoking are the commonest smoking habits. Factors considered for the study are tobacco usage (chewing and smoking) alcohol, mostly locally brewed from palm trees, (ethanol content 40%-60%), dietary habits (vegetarian / nonvegetarian) and literacy status. Vegetarians, in general do not consume poultry or fish products and avoid animal meat, The questionnaire included details of the habit, age started frequency per day and duration in years, and cessation of the habit. Unconditional logistic regression method was used to estimate the relative risk for factors. The relative risk estimates were obtained after stratification of factors by four age groups (<35yrs, 35-44 yrs, 45-54 yrs, 55 yrs+) and three areas of residence (Bombay, Maharashtra, Others).

RESULTS

General features like age, place of residence, religious distribution and habits of patients and controls are presented in Table I. The religious distribution of cancer patients and control did not differ and hence is not adjusted for in the analysis. Cancer patients and controls were in the age range of 25 years and 87 years. Base tongue cancer patients were found to be older about five years compared to anterior tongue cancer patients. Twenty three patients (16.2%) in anterior tongue (AT) group and 36 (7.3%) patients in base tongue (BT) group did not report any of the habits

Table II

RR estimates for chewers, smokers and alcohol users and tests of significance.*

Factors		controls	Ant. Tongue (AT)		Base Tongue (BT)	
			Case	RR	Cases	RR
A.	Chewers					
	Non Chewers	382	65	1.0	323	1.0
	Chewers	251	76	1.67 (1.12-2.51)	172	0.76NS (0.96-5.27)
	Not recorded	4	1		-	
B	Chewing Type					
	Non Chewers	382	65	1.0	323	1.0
	Tobacco Chewers	233	75	1.81 (1.21-2.73)	154	0.70 (0.5-0.9)
	Non Tobacco	11	0		14	1.32 NS (0.5-3.7)
	Others	5	1	0.67 NS (0.03-7.70)	4	0.60 NS (0.1-3.3)
	Not Recorded	4	1		-	
C.	Smoking					
	Non Smokers	336	72	1.0	91	1.0
	Smokers	295	69	0.97 NS (0.65-1.44)	404	4.34 (3.2-5.9)
	Not Recorded	4	1		-	
d.	Smoking Type					
	Non Smokers	337	73	1.0	91	1.0
	Bidi	186	53	1.12 NS (0.73-1.74)	360	5.90 (4.2-8.2)
	Cigarette	98	10	0.55 NS (0.24-1.15)	35	1.45 NS (0.9-2.5)
	Bidi + Cigarette	7	2	0.92 NS (0.12-5.43)	6	2.05 NS (0.5-8.4)
	Others	3	3	3.02 NS (0.44-21.3)	3	2.29 NS (0.3-19.6)
	Not Recorded	4	1		-	
e	Alcohol					
	Non User	509	102	1.0	382	1.0
	Alcohol User	122	39	1.79 (1.12-2.84)	113	1.45 (1.1-2.1)
	Not Recorded	4	1		-	

* - Stratified by 4 age groups and 3 areas of residence. NS - Not Significant
The figures in() indicate lower and upper Confidence Interval

considered in the study. Alcohol drinking was reported in 122 controls (19.4%), 39 (28.2%) patients in AT group and 113 (22.8%) patients in BT group. There was notable variation of habits with respect to two cancer groups. Among AT group, chewing habit was predominant (54%) whereas among BT group smoking habit was commonly observed (81%).

RR estimates for chewers, smokers and alchohol drinkers with confidence intervals are shown in Table II. Chewers had excess risk for anterior tongue cancer with relative risk (RR)1.81 (C.I. 1.2-2.7) whereas smokers had 4.3 times excess risk (C.I.3.2-5.9) for base tongue cancer. When categorised further, tobacco chewing emerged as a significant risk

Table III

RR for bidi smoking and use of alcohol and tests of significance according to frequency per day*

Factors	controls	Ant. Tongue (AT) # Case	RR	Base Tongue (BT)* Cases	RR
1. Bidi					
Non User	438	86	1.0	129	1.0
1 - 10 times	79	25	1.23 NS (0.69-2.2)	141	4.32 (3.04 - 6.7)
11 - 20 times	54	11	0.84 (0.78-1.78)	94	5.15 (3.39-8.5)
21 - 30 times	56	18	1.39 NS (0.72-2.67)	107	4.8 (3.2-7.7)
31 + times	4	1		24	14.3 (4.1-50.7)
Not Recorded	4	1		-	
2. Alcohol					
Non User	509	102	1.0	382	1.0
Once	108	27	1.46 NS (0.85-2.48)	99	1.51 (1.1-2.27)
Twice	14	12	3.70 (1.69-10.8)	14	1.14 NS (0.44-3.1)
Not Recorded	4	1		-	
3. Tobacco					
Non User	398	66	1.0	341	1.0
1 - 10 times	203	67	1.88 (1.24-2.87)	135	0.7 (0.5-9.5)
11- 20 times	28	7	1.65 NS (0.62-4.64)	14	0.5 NS (0.3-1.2)
21 - 30 times	1	1	8.3 (0.12-391.3)	1	1.1 NS (0.03-45.1)
31 + times	1	-		4	10.04 NS (0.5-209.40)
Not Recorded	4	1		-	

+ - Stratified by 4 age groups and 3 areas of residence
- Trend Significant for tobacco and alcohol
** - Trend Significant for bidi and alcohol*
NS - Not Significant; The figures in () indicate lower lower and upper Confidence Interval

for AT group only and bidi smoking was an important risk factor for BT group only. Cigarette smoking did not emerge as a significant risk factor for two sites. Alcohol drinking was found to be a significant risk factor for both subsites of tongue cancer and the estimated relative risk ranged between 1.45 and 1.79. Further the result of trend analysis with respect to frequency and duration of these habits for anterior tongue and base tongue cancers are separately shown in Table III and IV. The trend analysis again confirmed that the two habits namely bidi smoking and tobacco chewing showed statistically significant trends with the increse in the frequency and duration of the habits among BT and AT groups respectively. The trend analysis for duration of chewing habit was also statistically significant for anterior tongue cancer. Smokers who smoked bidi 31 times or more per day had about 14.3 times excess risk of getting base tongue cancer and the risk level for over 30 years of habit showed about 5 fold risk compared to non smokers. Cigarette smoking did not emerge as a risk factor for both groups either in terms of frequency or duration of the habit. The trend

Table IV

*RR estimates * for bidi smoking and use of alcohol and tests of significance according to duration @*

Factors		controls	Ant. Tongue Case	(AT) # RR	Base Tongue (BT)* Cases	RR
1.	Bidi					
	Non User	438	86	1.0	129	1.0
	1 - 10 yrs	63	7	0.52 NS (0.2-1.3)	30	2.2 (1.3 - 4.1)
	11 - 20 yrs	48	16	1.39 NS (0.7-2.7)	64	4.5 (3.1-8.7)
	21 - 30 yrs	39	12	1.24 NS (0.6-2.8)	123	7.7 (4.8-13.0)
	31 + yrs	43	20	1.61 NS (0.8-3.4)	149	5.1 (3.3-8.3)
	Not Recorded	4	1		-	
2.	Alcohol					
	Non User	509	102	1.0	382	1.0
	1 - 10 yrs	62	11	1.21 NS (0.6-2.6)	38	1.5 NS (0.9-2.5)
	11 - 20 yrs	35	12	2.0 (0.9-4.4)	35	1.6 NS (0.9-2.9)
	21 - 30 yrs	14	12	3.3 (1.4-8.9)	32	2.0 (1.0-4.6)
	31 + yrs	11	4	1.3 NS (0.3-4.8)	8	0.5 NS (0.2-1.4)
	Not Recorded	4	1		-	
3.	Tobacco					
	Non User	398	66	1.0	341	1.0
	1 - 10 times	93	20	2.04 (1.04-3.86)	28	0.5 (0.3-0.89)
	11- 20 times	51	25	3.58 (1.9-7.3)	31	0.9 (0.5-1.5)
	21 - 30 times	48	19	1.83 (0.92-3.6)	47	0.9 (0.5-1.4)
	31 + times	41	11	0.77 NS (0.33-1.77)	48	0.6 (0.4-0.99)
	Not Recorded	4	1		-	

+ - Stratified by 4 age groups and 3 areas of residence
*# - Trend Significant for tobacco & alcohol; *- Trend Significant for bidi & alcohol*
NS - Not Significant; The figures in () indicate lower and upper Confidence Interval

analysis for alcohol habit according to frequency and duration showed a statistically significant association with tongue cancer.

The literacy status and dietary factors were also analysed for the risk of these two sites after stratification by 4 age groups and 3 types of residence. The estimates were obtained without adjusting for tobacco and alcohol habits. Considering the risk among literate as unity, illiterates showed two fold risk (RR=2.1C. I.1.41-3.2) for AT cancer and 1.42 times excess risk (C.I. 1.08 - 1.93) for BT cancer. Patients who took non vegetarian diet were found to have two fold risk (RR =2.18C.I.1.27-3.84) for anterior tongue cancer only and for BT cancer there was a 34% significant reduction in risk with RR 0.66 (C.I. 0.48-0.89).

Table IV shows the unconditional logistic regression model for two cancer sites.

Table V

Unconditional logistic regression model using five factors for two sub sites of tongue*

Site / Factor	RR	Confidence Interval	P Value
Anterior Tongue (AT)			
Bidi (1=Yes; 0=No)	1.0	0.66 - 1.52	p = 0.998
Alcohol (1=Yeas; 0=No)	1.54	0.97 -2.44	P = 0.063
Illiteracy (1 = Yes; 0=No)	1.81	1.198 - 2.73	p =0.005
Nonvegerarian (1=Yes; 0=No)	1.74	1.014 -2.995	P =0.044
Tobacco Chewing (1= Yeas 0= No)	1.74	1.173 - 2.571	P = 0.006
Base Tongue (BT)			
Bidi (1=Yeas; 0=No)	4.69	3.51 - 6.27	P <.001
Alcohol (1=Yes; 0=No)	1.34	0.93 - 1.93	P =0.116
Illiteracy (1= Yes; 0=No)	1.22	0.90 - 1.66	P = 0.195
Nonvegetarian (1=Yes; 0=No)	0.59	0.43 - 0.83	P = 0.002
Tobacco Chewing (1= Yes; 0=No)	0.88	0.65 - 1.19	P = 0.402
Tongue (AT + BT)			
Bidi (1=Yes 0=No)	3.32	2.56 - 4.3	p <.001
Alcohol (1=Yes; = No)	1.38	0.99 - 1.9	p = 0.05
Illiteracy (1=Yes; 0=No)	1.41	1.08 - 1.85	P=0.013
Nonvegetarian (1=Yes; 0=No)	0.77	0.56 - 1.04	P = 0.089
Tobacco Chewing (1-Yes; 0=No)	1.13	0.87 - 1.47	P = 0.36

* - Adjusted for 4 age groups and 3 areas of residence

The model confirmed the significance of tobacco chewing, nonvegetarian diet, and illiteracy status for anterior tongue cancer. Bidi smoking emerged as a significant risk factor for the base tongue cancer with RR 4.69 (C.I. 3.51-6.27). The risk due to alcohol habit was higher than unity in both sites but not found to be statistically significant in this multivariate model.

DISCUSSION

Epidemiological research in recent times has become possible to address issues to the specific sites of cancer according to International Classification of Diseases (ICD 9th). Data on cancer incidence are being reported with certain accuracy upto the fourth digit rubrics of ICD. This retrospective case control study was carried out to evalute the association of tobacco and alcohol habits with respect to cancer in the base and oral tongue. Only histologically confirmed tongue cancer cases were included in this study. Not all of the tongue cancer patients diagnosed during the period could be interviewed, for many reasons. Controls were chosen from among the interviewed patients who were diagnosed as being free from cancer, infectious diseases and benign neoplams. The use of hospital controls instead of population controls may have affected the estimates of risk factors. Previous studies carried out in India, have identified risk factors for oral cancer (ICD 140-145) or for cancers of two or three sites of oral cavity[6,7,8,9,10]. In an earlier study from Bombay, the risk factors for individual sites of oral cavity, pharynx and larynx were analyzed and estimated but the study did not evaluate for alcohol and dietary factors[4].

The composition of habit pattern between control and cancer groups shows the predominance of smoking habit among BT group (81.6%) and chewing habit among AT group (54.2%). The study has brought out that the location of cancer in the tongue to some extent depends upon the type of tobacco habit. Bidi smokers in particualr had a higher risk for

Base Tongue cancer than for Ant. Tongue cancer. The dose response relationship was also established according to frequency and duration of bidi smoking habit for BT cancer and tobacco chewing habit for AT cancer. When the two cancer groups were combined, the model showed significant association of bidi smoking, alcohol, and illiteracy with tongue cancer. Tobacco chewing and nonvegetarian diet did not emerge as significant.

The average age of the patients with respect to two cancer group show variation. This is also observed from the Cancer Registry data of the hospital for the last five years[11]. Patients with AT cancer were found to be about five years younger compared to BT cancer patients in the hospital data also. Further studies are required to identify factors responsible for this.

Alcohol as a high risk factor has been reported for oral cavity cancer in general. Previous studies showed that alcohol habit is associated with oral cancer[5,7]. In this study also it has been shown to be associated with AT cancer but not with BT cancer. It is necessary to collect more information on alcohol habit in our population and also the type of liquor and quantity consumed to provide a meaningful estimate of the risk involved with oral cancer and in general for all cancer.

Many studies have identified the role of dietary factors in cancer of mouth, pharynx and larynx. The association of dietary factors with oral cancer in particular has been confirmed in the studies conducted from India. Non vegetarian diet compared to vegetarian diet seemed to increase the risk for AT cancer. Further studies are required to assess the risk factors among individual items of nonvegetarian diet after controlling the known protective factors.

Illiterates had a higher risk for anterior tongue cancer in our study. This may be due to the different life style, habits and customs, poor socio economic status, dietary habits and poor oral hygiene among illiterates compared to literates. These factors need to be considered in future studies. It is necessary to have a new strategy for cancer control and prevention for such high risk groups.

In conclusion, the study brings out that the location of cancer has got a direct bearing with the type of tobacco use and other related habits and this inturn may provide meaningful interpretation of variations observed in the incidence of tongue cancer around the world.

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ESTIMATE OF CANCER INCIDENCE IN INDIA IN 1991

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SUMMARY

Cancer incidence and eighteen site-specific age standardised rates in India were estimated for the year 1991. With the establishment of National Cancer Registry Programme, incidence rates per 100,000 are available from six metropolitan registries and one rural registry. Using population census data for India in 1991, about 609,000 new cancer cases were estimated to have been diagnosed in the country in 1991. The estimated age standardised rates per 100,000 were 96.4 for males and 88.2 for females. The five most common cancers were lung (10.6%) pharynx (9.1%), oesophagus (6.7%), tongue (6.6%) and stomach (5.7%) among males and cervix (23.5%), breast (19.3%), ovary (5.5%) oesophagus (4.4%), and mouth (3.9%) among females. A comparison of estimated ASRs for two two largest countries in Asia (China and India) showed differences in the pattern of cancer.

INTRODUCTION

The estimates of cancer incidence reported for the year 1985 indicated that there were 7.6 million cancer cases in the world and over 50% of them were diagnosed in the developing countries. In the Southern Asia region alone (India, Pakistan, Bangladesh, Srilanka and Iran) there were 806,000 cancer patients. The age standardised rates per 100,000 in 1985 for Southern Asia were 106.6 and 111.1 for males and females respectively[1]. With the establishment of National Cancer Registry Programme in India, it has been possible to identify cancer incidence in six selected metropolitan cities and in one rural area. This should help to assess cancer burden of the country. The purpose of this paper is to estimate the cancer incidence for the whole country in 1991 using available data.

PATIENTS AND METHOD

In India, a population census was carried out for the year 1991 for the various states in the country and there were 843,93,0861 (M = 437.1 million, F = 406.8 million) people in the country[2]. Due to non-availability of age and sex distribution of the population for each state, the relative frequencies of the broad age groups for the country were used namely, 12.8% for 0 to4 yrs, 22.9% for 5 to 14yrs, 57.7% for 15 to 59 yrs, and 6.6% for 60+ yrs[3]. The sex ratio for each state in the country has enabled us to estimate the general population of each state according to above specified age groups and sex distribution. The cancer incidence rates per 100,000 according to age, sex and sitewise were available for the year 1991 from the metropolitan cities (namely Delhi, Bhopal, Mumbai and Bangalore) and from Ahmedabad registry (1988-89), Madras registry (1982-91) and a rural registry at Barshi,

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Table - 1
Estimated incidence rates per 100,000 for five regions of India by age group and sex in 1991

Age (in years)	Northern[1] M	Northern[1] F	Central[2] M	Central[2] F	Eastern[3] M	Eastern[3] F	Western[4] M	Western[4] F	Southern[5] M	Southern[5] F	All Regions M	All Regions F
0-4	17.1	13.2	3.0	2.9	2.9	2.9	9.4	6.2	9.2	7.7	6.6	5.4
5-14	13.0	7.3	7.0	5.2	8.1	5.1	7.7	4.7	7.3	5.8	7.5	5.4
15-59	62.1	99.1	55.3	73.1	52.3	71.4	61.2	75.9	58.4	98.2	56.3	81.0
60+	538.5	465.5	622.0	331.9	606.7	324.8	517.9	340.1	474.6	412.2	558.1	359.8
% of Indian Population	7.3	6.8	24.7	23.7	25.9	26.1	19.4	19.5	22.7	23.9	100.0	100.0
ASR*	99.8	111.6	101.0	80.3	98.9	78.4	95.0	83.0	88.6	81.2	96.2	88.2

*Age standardised rate per 100,000
1 Delhi, Haryana, Punjab, Himachal Pradesh, Jammu & Kashmir and Chandigarh
2 Uttar Pradesh and Madhya Pradesh
3 Bihar, West Bengal, Orissa, Assam and North Eastern states (Tripura, Manipur, Meghalaya, Nagaland, Arunachal Pradesh, Mizoram and Sikkim)
4 Maharashtra, Gujarat, Goa, Rajasthan, Daman & Diu and Dadra & Nagar Haveli
5 Tamil Nadu, Kerala, Karnataka, Pondicherry, Andhra Pradesh, Lakshadweep and Andaman & Nicobar Island

Maharashtra (1988-92)[4]. The Delhi incidence data[5] were used to estimate the number of new cancer cases for northern states (Punjab, Haryana, Jammu & Kashmir, Himachal Pradesh and Chandigarh region). The Ahmedabad data[6] were used for the western states (Gujarath and Rajasthan) and Bhopal data[7] for the states, namely Uttar Pradesh, Madhya Pradesh, West Bengal, Bihar, Orissa and Assam. Similarly the Mumbai data[8] were used for the states of Maharashtra and Goa and Bangalore data[9] for Karnataka and Andhra Pradesh. Madras incidence data were used to estimate the number of cancer cases in the states of Tamilnadu, Kerala and Pondicherry[10]. Though cancer incidence of a metropolitan city in a state may not be a representative of the entire state or the region, it could be the best possible alternative available for the extrapolation. A special computer program was prepared to estimate the number of cancer cases for each state using one of the six representative registry data (4 age groups and sex). The crude incidence rates per 100,000 for each sex in seven registries were recalculated for the age groups (namely 0 to 4,5 to 14, 15 to 59 and 60+ yrs) and then multiplied by the corresponding age groups of state population to obtain the number of cancer patients. Since there were no representative incidence data available in the north eastern region (mostly rural areas - see Table I), rural registry incidence data available from Barshi were used to estimate the total number of cancer patients in that region. In order to estimate the frequency of eighteen site-specific cancers for each State, site and sex specific percentages published by one of the above mentioned seven registries were used. For the state of Assam, North Eastern States and Kerala, the site and sex specific percentages published by the hospital cancer registries at Dibrugarh in Assam[11] and at Trivandrum in Kerala[12] were used for the partition of total cancer cases. Age-specific incidence rates were estimated for four broad age groups: 0 to 4,5 to 14,15 to 59 and 60 +yrs. Age-standardised incidence rates for all sites and eighteen sites were calculated using the weights of the "world

Table - II

Estimated number of new cancer cases (thousands) and ASR rates by sites, sex and states in India 1991

	Tongue (141)		Mouth (143-145)		Pharynx (146-9)		Oesophagus (150)		Stomach (151)		Colon (153)		Rectum (154)		Larynx (161)		Lung (162)	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Uttar Pradesh	4.1	0.7	2.0	1.3	5.1	1.3	3.3	1.6	2.8	1.5	0.8	0.4	1.4	0.9	2.0	0.1	6.9	0.7
Bihar	2.6	0.5	1.2	0.8	3.1	0.8	2.0	1.0	1.7	0.9	0.5	0.3	0.8	0.6	1.2	0.1	4.2	0.5
Maharashtra	1.4	0.4	1.6	1.1	1.1	0.9	2.1	1.5	1.6	0.7	0.8	0.6	0.8	0.7	1.5	0.2	2.9	0.7
West Bengal	2.0	0.4	1.0	0.7	2.5	0.1	1.6	0.8	1.4	0.7	0.4	0.2	0.7	0.4	1.0	0.1	3.3	0.4
Andhra Pradesh	0.8	0.2	0.6	1.7	1.8	0.6	1.9	1.5	2.0	1.1	0.5	0.5	0.7	0.7	0.7	0.7	1.6	0.4
Madhya Pradesh	1.9	0.4	0.9	0.6	2.4	0.1	1.5	0.8	1.3	0.7	0.4	0.2	0.6	0.4	0.9	0.1	3.1	0.4
Tamilnadu	0.9	0.3	1.3	1.4	1.7	0.6	1.5	1.1	2.7	1.2	0.3	0.2	0.5	0.4	0.8	0.1	1.8	0.3
Karnataka	0.5	0.1	0.4	1.1	1.2	0.4	1.3	1.0	1.4	0.8	0.4	0.3	0.5	0.5	0.5	0.1	1.1	0.3
Rajasthan	1.5	0.3	0.9	0.3	2.0	0.4	1.0	0.6	0.3	0.2	0.2	0.2	0.4	0.3	1.0	0.1	1.7	0.3
Gujarat	1.4	0.2	0.8	0.3	1.8	0.4	0.9	0.6	0.3	0.2	0.2	0.2	0.4	0.3	0.9	0.1	1.6	0.3
Orissa	0.9	0.2	0.4	0.3	1.1	0.0	0.7	0.4	0.6	0.4	0.2	0.1	0.2	0.2	0.4	0.0	1.5	0.2
Kerala	0.6	0.2	1.1	1.1	0.6	0.1	0.6	0.3	0.5	0.2	0.2	0.1	0.3	0.2	0.5	0.0	1.1	0.2
Assam	0.7	0.3	0.3	0.4	2.6	0.8	1.4	1.0	0.4	0.2	0.1	0.1	0.2	0.1	0.3	0.1	0.8	0.1
Punjab	0.5	0.1	0.3	0.2	0.5	0.1	0.4	0.2	0.3	0.1	0.2	0.1	0.2	0.1	0.6	0.1	0.8	0.1
Haryana	0.4	0.1	0.2	0.1	0.4	0.1	0.3	0.2	0.2	0.1	0.1	0.1	0.2	0.1	0.5	0.1	0.7	0.1
Delhi	0.2	0.0	0.1	0.1	0.2	0.0	0.1	0.1	0.1	0.1	0.1	0.0	0.1	0.1	0.2	0.0	0.3	0.0
Jammu & Kashmir	0.2	0.1	0.1	0.1	0.2	0.0	0.1	0.1	0.1	0.1	0.1	0.0	0.1	0.1	0.2	0.0	0.3	0.1
Himachal Pradesh	0.1	0.0	0.1	0.0	0.1	0.0	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.0
Goa	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Others	0.1	0.0	0.1	0.0	0.3	0.0	0.2	0.1	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.0
Total	20.8	4.8	13.4	11.6	28.7	6.7	21.0	13.0	17.8	9.2	5.5	4.6	6.2	5.1	13.4	1.4	33.3	5.1
% of Total	6.6	3.6	4.3	8.9	9.1	5.2	6.7	9.4	5.7	7.1	1.7	3.5	2.0	3.9	4.3	1.1	10.6	3.9
ASR Rates	6.5	1.4	3.9	3.9	8.7	1.5	6.5	4.1	5.0	2.8	1.8	1.3	2.0	2.0	4.2	0.4	10.4	1.6
% of Grand Total	4.2		4.1		5.8		5.6		4.4		1.2		2.2		2.6		9.3	

Estimated number of new cancer cases (thousands) and ASR rates by sites, sex and states in India 1991

	Breast (174)	Cervix (180)	Uterus (182)	Ovary (183)	Prostate (185)	Bladder (188)		Kidney (189)		Lymphoma 200-203)		Leukemia 204-208)		All Sites		
	F	F	F	F	M	M	F	M	F	M	F	M	F	M	F	T
Uttar Pradesh	5.9	11.5	2.9	2.9	2.3	1.5	0.6	2.1	0.3	3.2	2.6	2.5	1.6	54.4	42.6	97.1
Bihar	3.6	7.1	2.6	1.8	1.4	0.9	0.4	2.1	0.2	1.4	1.6	1.5	1.4	32.5	27.5	60.3
Maharashtra	7.6	8.2	0.6	1.7	1.2	0.8	0.2	0.5	0.3	1.7	1.3	1.1	0.9	29.1	20.2	49.3
West Bengal	4.5	5.5	2.4	1.4	1.1	0.7	0.3	2.1	0.1	1.1	1.4	1.1	0.9	26.2	21.6	47.8
Andhra Pradesh	5.2	6.1	2.5	1.2	0.9	0.8	0.2	2.3	0.2	1.5	1.2	1.2	0.8	22.6	28.2	50.8
Madhya Pradesh	4.4	5.4	0.6	1.4	1.1	0.7	0.3	2.1	0.1	1.1	1.4	1.1	0.9	25.5	20.9	46.3
Tamilnadu	4.5	6.2	2.3	1.1	0.4	3.4	0.1	3.2	0.1	1.3	1.5	1.1	0.4	19.2	23.7	43.1
Karnataka	3.6	4.1	2.3	0.8	2.6	0.6	0.1	3.2	0.1	2.6	2.6	1.1	0.6	22.4	16.6	39.2
Rajasthan	2.4	3.2	2.2	0.4	0.3	0.5	0.1	2.1	0.1	2.6	2.3	1.6	0.3	16.6	11.7	28.3
Gujarat	2.3	2.7	0.2	0.4	0.3	0.4	0.1	2.1	0.1	2.6	2.3	2.6	0.3	18.4	11.1	29.5
Orissa	2.1	3.6	2.2	0.7	0.5	0.3	0.1	2.0	0.1	2.5	2.2	2.5	2.1	11.5	10.1	21.6
Kerala	2.9	2.5	0.2	0.7	0.2	0.2	0.0	2.1	0.1	2.5	2.4	1.5	0.4	9.8	12.7	22.5
Assam	0.9	1.1	0.0	0.3	0.0	0.1	0.0	0.0	0.0	2.5	2.2	1.2	0.1	3.6	7.2	10.8
Punjab	1.9	1.8	0.1	0.6	0.3	0.4	0.1	2.1	0.1	2.7	2.4	1.6	0.3	5.6	5.8	11.4
Haryana	1.5	1.4	0.1	0.5	0.3	0.3	0.1	2.1	0.1	2.6	2.3	1.4	0.3	5.3	7.1	14.0
Delhi	0.7	0.7	0.1	0.2	0.1	0.1	0.0	2.0	0.0	2.5	2.1	1.2	0.2	2.2	2.3	4.5
Jammu & Kashmir	0.6	0.7	0.1	0.2	0.1	0.1	0.0	2.0	0.0	2.5	2.2	1.2	0.2	3.2	3.4	6.6
Himachal Pradesh	0.5	0.5	0.0	0.1	0.1	0.1	0.0	2.0	0.0	2.2	2.1	1.2	0.1	2.0	2.4	4.4
Goa	0.1	0.1	2.0	2.0	0.0	0.0	0.0	2.0	0.0	2.0	2.0	2.1	2.0	2.1	2.0	2.3
Others	0.3	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.1	2.1	2.0	2.0	2.5	2.4	5.9
Total	52.6	69.2	5.2	16.3	11.2	8.5	2.7	2.1	1.9	15.1	2.1	16.5	6.2	354.6	294.4	649.0
%of Total	19.3	23.5	1.8	5.5	3.6	2.8	0.9	0.7	0.6	4.8	2.9	5.4	2.1	54.7	45.3	
ASR Rates	17.5	19.6	1.4	4.5	4.0	2.8	0.9	0.7	0.7	3.8	2.4	3.9	1.7	96.4	68.2	
% of Grand Total	10.0	11.4	0.9	2.7	1.8	1.9		0.7		2.8		3.8				

Figures in () indicate ICD-9 codes.

Table - III

Ten leading sites of cancer in India in 1991 - estimated numbers (thousands) and percentage of total

Males				Females				Both Sexes			
Rank	Site	Number	%	Rank	Site	Number	%	Rank	Site	Number	%
1	Lung	33.3	10.6	1	Cervix	69.2	23.5	1	Cervix	69.2	11.4
2	Pharynx	28.7	9.1	2	Breast	60.6	19.3	2	Breast	60.6	10.0
3	oesophagus	21.0	6.7	3	Ovary	16.3	5.5	3	Lung	38.4	6.3
4	Tongue	20.8	6.6	4	Oesophagus	13.0	4.4	4	Pharynx	34.7	5.8
5	Stomach	17.8	5.7	5	Mouth	11.6	3.9	5	Oesophagus	34.0	5.6
6	Leukaemia	16.9	5.4	6	Stomach	9.2	3.1	6	Stomach	27.0	4.4
7	Lymphoma	15.1	4.8	7	Lymphoma	8.1	2.8	7	Tongue	25.6	4.2
8	Larynx	13.4	4.3	8	Pharynx	6.7	2.8	8	Mouth	25.0	4.1
9	Mouth	13.4	4.3	9	Leukaemia	6.2	2.1	9	Lymphoma	23.2	3.8
10	Prostate	11.2	3.6	10	Rectum	6.1	2.1	9	Leukaemia	23.1	3.8

standard'' population (0.12.0.19.0.58 and 0.11 for 0 to 4.5 to 14.15 to 59. 60+ yrs age groups respectively). Thus cancer incidence for the whole country was estimated by the use of region specific estimates, similar to the method used in the estimation of Worldwide Incidence for the year 1985[5].

RESULTS

The whole country has been broadly divided into five regions as shown in Table 1. The estimated incidence rates per 100,000 according to four age groups, sex and regionwise are presented. In India, the estimated age-standardised incidence rates per 100,000 adjusted to world population, were 96.4 for males and 88.2 for females. The ASR's were higher in both sexes in northern region (M-99.8, F-111.6) and in males in central regions (M-101.0), compared to the rates in other regions of the country.

The total number of cancer patients for the whole country in 1991 is estimated to be around 0.609 million (0.315 million males and 0.294 million females). The number of female cancer patients is found to be more than the number of male cancer patients in the state of Maharashtra, Andhra Pradesh, Karnataka, Tamil Nadu and Kerala, partly due to high frequency of uterine cervix cancer. The estimated number of cancer cases by State varied from 900 cases in Goa to 97,000 cases in Uttar pradesh.

Table II shows the estimated number of cancer cases (in thousands) by site, sex and statewise in India and Age Standardised Rates (ASR) per 100,000 adjusted to world population. Eighteen site-specific cancer together constitututed around 0.216 million males (68.7% of total male cancer) and 0.231 million female cancers (78.5% of total female cancer) in the country.

Among the ten most common cancers, (Table - III) lung cancer was the most common cancer among males in India with 33,300 new cases, or 10.6% of the total and the leading site in males in a majority of States in India (Table II). The ASR for lung cancer is estimated to be 10.4 per 100,000 for males and 1.6 per 100,000 for females (Table II). When both sexes are combined, lung cancer ranks third with 38,400 cases in India.

Pharyngeal cancer was the second most common cancer among males (9.1% of the total). The relative frequency of pharyngeal cancer among males was higher than lung cancer in the State of Assam. Oesophageal cancer is the

third leading site among males (21,000 new cases, 6.7% total male cancer) and fourth leading site among females (13,000, 4.4% of total female). Tongue cancer (20,800 new cases, 6.6% of total male) is the fourth leading site among males and it is higher in rank order than mouth cancer. When both sexes are combined together, tongue cancer accounted for 25,600 new cases in India. Among females, tongue cancer forms about 1.6% of total female cancer and does not figure among the ten leading sites in females. The estimated ASR for tongue cancer is 6.3 per 100,000 in males and 1.4 per 100,000 in females.

Stomach cancer ranks fifth among males and sixth among females and accounts for 27,000 new cases (4.4% of total cancer) in India. The estimated ASR's are 5.0 and 2.8 per 100,000 for males and females respectively.

Cervix cancer is the first in frequency not only among females but also both the sexes together and accounts for 69,200 new cases in India. The estimated ASR is 19.9 per 100,000 and it forms about 23.5% of total female cancer. Breast cancer is the second most frequent cancer in females and ranks second overall when both sexes are considered together (10% of total cancer). The ASR is 17.5 per 100,000 and accounts for 60,600 new cases in India (19.3% of total female cancer). The estimated number of cases according to states in India showed an excess in frequency of breast cancer cases over cervix cancer in seven states in India (Table II).

The purpose of comparing ASRs for selected sites of cancer in India and China (Table IV) is to highlight possible differences in the pattern of cancer in these regions. The age distribution of the two populations is more or less similar, more so in the 65+ yrs group (India 3.9% China 5.3%)[1]. There are differences in ASR for the common cancers between the two countries more prominent for males and for cancers of lung, stomach, oesophagus and colon and rectum among both sexes. Further, the rates of all individual sites of cancer in males were higher in China than in India except for mouth, larynx and prostate cancers.

DISCUSSION

Cancer incidence and eighteen site-specific age-standardised incidence rates were estimated for the whole country in 1991 by using seven registries data. The methodology of using incidence data from selected areas or populations to the whole country has already been described. In order to estimate the cancer incidence in Southern Asia in 1985, weighted average of only three metropolitan registries (Mumbai, Madras and Bangalore) and one rural registry (Barshi) incidence data were used for the estimation of cancer incidence in India compared to the present study. The reliability and validity of these estimates are difficult to measure in the absence of complete data for the entire country. Non availability of age and sex distribution of the population for each state might have affected the estimates. In India Cancer incidence data are available in selected metropolitan cities only except for one rural registry. The use of urban incidence data for majority of states in India could possibly over estimate the number of cancer cases.

Assuming that the estimated crude rates for Southern Asia in 1985 (M=71.6, F= 79.5) remained the same in 1991 also, the expected number of cancer cases in Indian population would be around 0.636 million (Males =0.313, F= 0.323) which would be higher than our estimate. Based on the weighted average of incidence rates available from registries like

Table - IV
Comparision of ASR of selected sites in India with China 'and Southern Asia'

ICD-9	Site	Males			Females		
		China (1985)	Southern Asia (1985)	India (1991)	China (1985)	Southern Asia (1985)	India 1991
140-149	Mouth	8.7	25.1	18.9+	6.0	14.9	6.9+
150	Oesophagus	22.1	9.1	6.5	12.1	7.1	4.1
151	Stomach	43.1	7.5	5.0	19.4	4.0	2.8
153-154	Colon & Rectum	10.5	4.3	4.2	10.3	3.5	3.2
161	Larynx	2.8	7.6	4.2	1.1	1.3	0.4
162	Lung	28.3	13.2	10.4	12.1	2.2	1.6
174	Breast	-	-	-	14.6	19.1	17.5
180	Cervix	-	-	-	17.8	29.1	19.9
182	Uterus	-	-	-	4.2	1.8	1.4
183	Ovary	-	-	-	4.1	4.7	2.5
185	Prostate	1.2	3.5	4.0	-	-	-
188	Bladder	6.1	2.9	2.8	2.7	0.6	0.5
189	Kidney	2.1	1.2	0.7	1.7	0.6	0.7
200-203	Lymphoma	5.9	4.8	3.8	4.2	2.6	2.4
204-208	Leukaemia	5.9	2.7	3.9	4.4	1.7	1.7
140-208	All Sites	189.6	106.6	96.4	158.6	111.1	88.2

+ excludes site ICD 140 & 142

Mumbai, Bangalore, Madras, Bhopal, Delhi and Barshi for 1989, the number of cancer cases in India in 1992 was estimated to be around 0.644 million[13]. Instead of urban incidence data for the estimation, if one applies only the rural registry incidence data, the number of cancer cases in India would be around 0.349 million, probably an under estimate. Using the average of three metropolitan registries incidence data, namely Madras, Mumbai and Bangalore for the period 1982-84, in the year 1991, there would be around 0.331 million male cancers and 0.371 million female cancers cases in the country[14]. This is much higher than our estimate, perhaps due to differences in the method of estimation, and the use of population projections instead of actual data used in our study.

A comparison of cancer occurrence in the two largest countries (i.e. India and China) suggests that the cancer pattern and problems are quite different. This in turn makes it difficult to have uniform policy and programme to combat cancer for developing countries. The observed differences gives impetus to the need to identify the risks and protective factors in the two population.

Eighteen site-specific age-standardized rates for the whole country has been estimated for the first time in India. The use of four age groups namely 0-4,5-14,15-59 and 60+ may not be the most appropriate for estimating age-standardised rates. As it is well known, the first two strata would account only for three percent of total cancer. In order to assess the possible bias due to this, published ASR for all sites in Mumbai Registry for one year was recalculated using these four age strata for standardisation. The rates were 10%-13% less than the observed rates.

In males, the most common cancers namely lung, pharynx, oesophagus, tongue, larynx and mouth cancers whach accounted for 41.6% of the cases are known to be associated

with tobacco chewing and smoking[4,15,16,17,18,19,20,21,22]. Even in females, the tobacco-related cancers (oesophagus, mouth and pharynx cancer) accounted for 31.3% of the cases. It is not surprising that these cancers emerged as most common cancers since tobacco habit, in varying forms, are prevalent in many parts of the country.

Cervix cancer is the leading site of cancer in females and in most of the registries in India. Case-control studies indicated that early age at marriage, early age at first pregnancy, four or more number of pregnacies and lack of genital hygiene were high risk factors for cancer of the cervix[23]. In a rural set up, mass education on cancer awareness and symptoms was shown to have greatly contributed in downstaging of cancer of the cervix[24]. This should be taken as a guideline for implementing such programmes on a national level.

Breast cancer is the second commonest cancer among females in India. Recently, Mumbai and Delhi registry data showed that breast cancer has become the number one cancer, superseding cervix cancer. Though breast cancer incidence in India is two to three times lower than the incidence in western countries, factors like single women, late age at marriage and consequently the late age at first pregnancy and two or less number of pregnancies were found to increase the risk in Indian women[25]. Though mass screening of high risk women by annual mammography and physical examination may have a reduction in mortality, but in a country like India, self breast examination would be more suitable and convenient to have the desired effect. These estimates of cancer load could provide guideline and scope for proper planning of health needs, necessary infrastructure required in terms of health personnel, medical technology and allocation of funds for primary and secondary prevention.

With the identification of the common cancers in the country, priorities should include screening programmes for early detection and secondary prevention in cancers of the cervix and breast, the two most common cancers among women.

With the help of voluntary organisations and Government legislation, many tobacco related cancers, which account for almost two-fifth of total male cancers and one-third of total female cancers, can be prevented.

Assuming that there would be no major change in the habits and customs in the immediate future, and based on the population projections[1], it has been estimated that cancer load in the country would likely to reach a figure of 0.75 million in 2001 A.D. and 0.87 million in the year 2011 A.D.

There is an urgent need for Government and health personnel to take immediate steps in cancer control and prevention.

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Role of reproductive factors in breast cancer in a low-risk area: a case–control study

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Summary A case–control study of 689 breast cancer patients seen at Tata Memorial Hospital during the period 1980–84 was carried out. During the same period 711 females who attended the hospital without a history of benign breast lesions or gynaecological complaints were selected as controls. Patients were interviewed by trained investigators to collect data on reproductive factors, menstrual history, tobacco smoking and chewing habit, dietary practices (vegetarian and non-vegetarian diet) and alcohol consumption. Cases and controls were stratified into four age groups (<35 years, 35–44, 45–54 and 55+ years) and three places of residence (Bombay, Maharashtra, others). The adjusted relative risk (RR) for unmarried women compared with married women was 2.3. Nulliparous women had a 2.2-fold higher risk than parous women. Late age at marriage (30 years and above) and late age at first pregnancy (30 years and above) showed excess risks of 2.5 and 5.4 compared with women married at the age of 14 years and age at first pregnancy of ≤14 years. Three or more pregnancies was associated with a 40–50% reduction in risk ($P<0.01$). Non-vegetarian diet, literacy status and a history of stillbirth and abortion did not emerge as significant risk factors for breast cancer in our study. These findings, in a low-risk population, were consistent with those reported from high-risk populations.

Cancer of the breast is the leading cancer among women in developed countries, whereas it is the second commonest cancer among women in developing countries. There has been a steady increase in the incidence of breast cancer all over the world, but the mortality from breast cancer has remained constant. In Bombay, females have a lifetime risk of breast cancer of around 1 in 35 compared with one in six in the USA (NCRP, 1992). Case–control studies on breast cancer carried out in various parts of the world have highlighted the association with certain female reproductive factors, diet and familial history of cancer (MacMahon *et al.*, 1970*a,b*; Adami *et al.*, 1990; Wynder *et al.*, 1991). Parkin *et al.* (1993) estimated that 298,000 breast cancer cases were recorded during the year 1985 in developing countries. Though a large number of women are affected with breast cancer, very few studies have been undertaken to identify the risk factors for breast cancer in developing countries. This study has been carried out to identify the association of reproductive factors with breast cancer in a low-incidence population.

Materials and methods

Patients attending Tata Memorial Hospital, before being medically examined, are interviewed by our social investigators. The questionnaire contains items on demographic factors, family history, age at menarche, age at marriage, number of pregnancies, history of stillbirth and abortion, family planning practices and menstrual history. In addition, data on tobacco smoking and chewing, dietary practices and alcohol habit were also collected. Data on dietary practices are restricted to two major groups, vegetarian and non-vegetarian. During 1980–84, 689 female breast cancer patients were interviewed. Females who were referred to our hospital for suspected malignancies, mostly in the mouth and throat, and found to be free of cancer were considered as controls. Among the female patients who were interviewed during the period, 711 females were found to be eligible as controls. Cases and controls were stratified into four age groups (<35 years, 35–44, 45–54, 55+ years) and three places of residence (Bombay, Maharashtra, others). Odds ratios were calculated by univariate methods as well as by stratified analysis. The Mantel and Haenszel (1959) summary chi-squared test was used for testing statistical significance and a test-based estimation procedure was used for calculation of confidence intervals for odds ratios (Kleinbaum *et al.*, 1982).

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Results

General features of breast cancer cases and controls are shown in Table I. The average age of cancer patients was 46.2 years, whereas it was 42.8 years for controls. The religious distribution between cases and controls did not differ and hence is not adjusted for in the analysis. Reproductive factors in cases and controls are presented in Table II. Factors such as age at menarche, age at marriage, age at first pregnancy and number of pregnancies appeared to be similar between the cancer cases and controls.

The relative risks (RRs) for factors studied are presented in Table III. Cases and controls were stratified by four age groups and three places of residence. In our study, unmarried women had a 2.3 times higher risk of developing breast cancer than married women. The nulliparous women had 2.2 times the risk of parous women ($P<0.001$). Breast feeding.

Table I General features of breast cancer cases and controls 1980–84

	Cases (%)	*Controls (%)*
Number	689	711
Average age at presentation (years)	46.2	42.8
Standard deviation	10.6	10.0
Residennal status		
Bombay	294 (42.7)	383 (53.9)
Maharashtra (excluding Bombay)	229 (32.1)	225 (31.6)
Others	174 (25.2)	103 (14.5)
Marital status		
Unmarried	22 (3.2)	11 (1.5)
Married	491 (71.3)	579 (81.4)
Widowed	174 (25.2)	114 (16.1)
Divorced	2 (0.3)	7 (1.0)
Religion		
Hindu	537 (77.9)	565 (79.5)
Muslim	96 (13.9)	97 (13.6)
Christian	37 (5.4)	34 (4.8)
Other	19 (2.8)	15 (2.1)

non-vegetarian diet and literacy status were not statistically significantly related to risk of developing breast cancer in our study group.

A history of abortion and stillbirth among eligible cases and controls was also studied for the risk of breast cancer. Seventy-one cases and 97 controls reported one or more abortions. The relative risk for women with a history of abortion was 0.8 (CI 0.59–1.09) compared with those with no history of abortion, and this was not statistically significant. Ten cases and 12 controls had a history of stillbirths. The relative risk was 0.9 (CI 0.61–1.37) and the difference was not statistically significant.

The relative risk estimates for factors such as age at menarche, age at marriage, age at first pregnancy and number of pregnancies are presented in Table IV. Owing to the small number of cases in some of the categories, it was not possible to adjust for age and place of residence. Hence relative risks were calculated for an unadjusted group only. Age at menarche after 15 years compared with 14 years and below did not show statistically significant differences for breast cancer risk. Women married after 30 years of age showed a 2.5 excess risk of breast cancer compared with women married before 15 years of age ($P<0.01$) For women with a first pregnancy after 30 years of age the relative risk was 5.4 compared to women with a first pregnancy before 15 years of age. Three or more pregnancies was associated with

Table II Reproductive factors among cases and controls

	Cases	*Controls*
Number	689	711
Average age at menarche[a]	13.9	13.8
Standard deviation	1.3	1.4
Average age at marriage[b]	16.8	16.7
Standard deviation	4.8	4.2
Average age at first pregnancy[c]	20.4	19.8
Standard deviation	4.3	3.5
Average number of pregnancies[d]	4.3	4.5
Standard deviation	2.1	2.1

[a]In 13 controls and 15 cases, age at menarche was not recorded. [b]In six cases and four controls the age at marriage was unknown. [c]Eight cases and nine controls unknown. [d]In one case and one control the number of pregnancies was unknown.

Table III Relative risk (RR) estimate for factors and their confidence intervals

Risk factors studied	*Cases factor/ non-factor*	*Controls factor/ non-factor*	*RR[a] (adjusted)*
Marital status			
Unmarried/ever married	22.667	11.700	2.26* (1.01–5.06)
Parity status[b]			
Nulliparous/parous	61.603	32.667	2.2*** (1.4–3.3)
Breast feeding[c]			
No/yes	17.579	11.653	2.02 NS (0.8–4.9)
Stillbirth[d]			
Yes/no	10.653	12.687	0.9 NS (0.6–1.4)
Abortion[e]			
Yes/no	71.593	97.602	0.8 NS (0.6–1.1)
Food habits			
Non-vegetarian/ vegetarian	484.202	543.164	0.8 NS (0.6–1.1)
Literacy status	295.394	326.385	1.1 NS (0.87–1.4)
Literate/illiterate			

[a]Stratified for four age groups (<35, 35–44, 45–54 and >55 years) and three places of residence (Bombay, Maharashtra and other). [b]Seven cases and three controls not recorded. [c]Three cases and one control was not recorded. [d]Four cases and one control not recorded. [e]Three cases and one control not recorded. [f]Three cases and four controls not known. Figures in parentheses indicate lower and upper confidence interval. ***$P<0.001$. NS, not significant. Non-factor = reference category = RR = 1.0. *$P<0.05$

Table IV Relative risk (RR) estimate for factors and their confidence intervals

Risk factors studied	*Cases*	*Controls*	*RR unadjusted*	*χ^2 for trend*
Age at menarche (years)				
⩽14	277	293	1.0	
15	171	203	0.9 NS (0.7–1.2)	
16	148	136	1.2 NS (0.9–1.5)	
17	63	47	1.4 NS (0.9–2.1)	
18	8	9	0.9 NS (0.3–2.5)	
19	7	10	0.7 NS (0.3–1.9)	$P>0.05$
Age at marriage (years)				
⩽14	194	188	1.0	
15–19	310	346	0.8 NS (0.7–1.1)	
20–24	119	128	0.9 NS (0.7–1.2)	
25–29	22	28	0.8 NS (0.4–1.4)	
30+	16	6	2.5** (1.0–6.6)	$P<0.05$
Age at first pregnancy				
⩽14	17	28	1.0	
15–19	265	317	1.3 NS (0.7–2.6)	
20–24	235	250	1.5 NS (0.8–2.9)	
25–29	55	63	1.4 NS (0.7–2.9)	
30+	30	9	5.4** (2.2–13.9)	$P<0.004$
No. of pregnancies				
Nulliparous	61	32	1.0	
One	45	33	0.7 NS (0.3–1.3)	
Two	86	74	0.6 NS (0.4–1.0)	
Three	115	121	0.5** (0.3–0.8)	
Four	111	135	0.4*** (0.3–0.7)	
Five	94	119	0.4*** (0.3–0.7)	
Six plus	155	184	0.5** (0.3–0.7)	$P<0.0001$

NS, not significant. **$P<0.01$. Figures in parentheses indicate lower and upper confidence intervals.

a significant reduction in breast cancer risk compared with nulliparity.

Discussion

Breast cancer is the second commonest cancer among females in developing countries, including India. Many case–control studies have been carried out in developed countries where breast cancer has been the most common cancer among females. It would be interesting to note whether established high-risk factors also play a significant role in a low-incidence area. An attempt has been made to identify high-risk groups and the role of reproductive factors in breast cancer.

Cases and controls were generally interviewed by our social investigators before medical examination. This helped to eliminate any interviewer bias in the collection of data.

Hospital controls were used instead of population controls. In the selection of controls, care was taken to include females without any history of either benign breast lesions or any gynaecological complaints. For a number of different reasons not all patients with breast cancer registered during the period could be interviewed. These are some of the limitations of the study which may or may not have affected the relative risk estimates.

The positive aspect is that the number of cases and controls is sufficient to detect a 2-fold increased risk even for factors with 90% power when such differences exist (Schlesselman, 1974).

Unmarried women and nulliparous women had a 2-fold increased risk for breast cancer. Also, late age at marriage (30 years and above) and late age at first pregnancy (30 years and above) were found to be risk factors for breast cancer. Multiparous women with three or more pregnancies had a 40–50% reduction in risk of breast cancer compared with nulliparous women. These findings are consistent with earlier reported studies from high-risk populations.

Paymaster and Gangadharan (1972) in a case-by-case matched case–control study on women from western India also showed that factors such as marital status, age at marriage, parity status, age at first delivery and number of pregnancies are associated with the risk of breast cancer.

The association of alcohol and dietary factors with breast cancer has also been reported in a high-incidence population (Schatzkin *et al.*, 1987; Willet *et al.*, 1987). In India, women in general do not indulge in alcohol in the same way as men. So, because of the negligible number of cases and controls with this habit, the effect of alcohol could not be studied. In our study we did not collect data on dietary factors, but information on type of food (i.e. vegetarian or non-vegetarian diet) consumed was collected for cases and controls. The risk level for non-vegetarians was lower than for vegetarians, but the difference was not statistically significant. Vegetarians who totally avoid animal meat, fish and poultry products generally consume less fat than non-vegetarians. In this context, the odds ratio was expected to be higher among the non-vegetarian group than among the vegetarian group since a diet with a high animal fat intake has been shown to increase the risk of breast cancer. Further studies are required to identify the association of dietary factors in breast cancer.

Moore *et al.* (1971) identified certain virus-like particles in the milk samples from the Parsis women in Bombay. However, further studies have not been done to confirm the viral aetiology (Gangadharan *et al.*, 1975).

The incidence of breast cancer is low in India compared with developed countries, but the rates are increasing (Yeole *et al.*, 1990). Cancer of the cervix uteri is the major leading site among females in most of the metropolitan registries in India, except in Greater Bombay, where for the last 10 years female breast cancer has been the leading site of cancer (Jussawala *et al.*, 1992).

Recently Jayant (1986) reported that the increase in the incidence of breast cancer in Bombay is not due to a cohort effect, unlike the decrease in incidence of cervix cancer.

The trends in incidence rates for the Bombay population over the years 1964–85 show that crude, age-adjusted and truncated rates are increasing at the rate of 1–1.5% and in all the age groups except those aged 35–44 years (Yeole *et al.*, 1990). The increase in incidence of breast cancer can be partly explained by changes in lifestyle, such as an increase in the number of 'unmarried women', later age at marriage and consequent later age at first pregnancy. Further studies are necessary to explain the role of dietary factors in breast cancer. With the change in lifestyle, smaller families and better socioeconomic advancement, the incidence of breast cancer is bound to increase over the years. In a developing country like India, with a large female population in high-risk groups, known methods of early detection such as mass screening and compulsory mammography may not be economically viable. However, propagation of breast self-examination may be important in helping to combat this health problem.

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Alcohol as an Additional Risk Factor in Laryngopharyngeal Cancer in Mumbai—A Case-Control Study

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ABSTRACT: A retrospective case-control study of 1698 male pharyngeal and laryngeal cancers seen at the Tata Memorial Hospital, Mumbai from 1980 to 1984 was undertaken to assess the association between the cancers and chewing, smoking, and alcohol habits. Male controls were chosen from persons who attended the hospital during the same period and who were diagnosed as free from cancer, benign tumor, and infectious disease. Statistical analysis was based on unconditional logistic regression method. Bidi smoking and alcohol drinking emerged as significant factors for pharyngeal and laryngeal cancers. Illiterates had 50 to 60% excess risk for pharyngeal cancer only. Nonvegetarian diet did not emerge as significant factor in our study.

KEY WORDS: alcohol, larynx, literacy, pharynx, tobacco, vegetarian diet.

I. INTRODUCTION

The association of tobacco chewing and smoking with head and neck cancer, in particular pharyngeal and laryngeal cancers, has been reported from the studies carried out in Mumbai, India.[1–3] Previous studies also estimated the odds ratio of tobacco chewing and smoking for individual sites of head and neck cancer. Many studies carried out in developed countries have shown cigarette smoking and alcohol as major risk factors for pharyngeal and laryngeal cancers.[4–8] In India, due to the paucity of data, the association of alcohol with pharyngeal and laryngeal cancers has not been studied in detail, and the few studies reported did not establish the dose-response relationship.[9] Alcohol drinking emerged as a significant risk factor in Indian population for oral cancer after adjusting for other known factors.[3] Available data from five metropolitan cancer registries in India indicate that there are variations in the age-adjusted incidence rates of oropharyngeal (males: 2.0–4.5 per 100,000), hypopharyngeal (4.2–9.9 per 100,000), and laryngeal (5.0–12.9 per 100,000) cancer. The incidence rates for laryngeal cancer are higher than the rates for oropharyngeal and hypopharyngeal cancer in almost all registries.[10,11] The aim of the study is to individually assess the role of alcohol, tobacco, diet, and literacy status in cancers of the pharynx and larynx, and to identify any excess risk due to these factors especially for laryngeal cancer in Indian population.

II. PATIENTS AND METHOD

This is a retrospective unmatched case-control study of patients who attended the hospital during the period from 1980 to 1984. Two trained social investigators interviewed the patients, at the time of registration but before clinical examination, in the outpatient department. The questionnaire contained data items on demographic factors, family history of cancer, tobacco habits, use of alcohol, frequency per day, duration in years, cessation of these habits, and di-

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etary practices. Medical records were scrutinized later for diagnosis and entered in the proforma. Among the cancer patients interviewed during the period were 1698 male patients with the histologic confirmation of cancer in pharyngeal and laryngeal regions. Cancer patients were classified into three major groups according to ICD-9 category. The oropharynx group included cancers of base tongue (ICD-1410), soft palate (ICD-1453), and oropharynx NOS (ICD-146). The hypopharynx group included cancers of post cricoid (ICD-1480), pyriform fossa (ICD-1481), and hypopharynx NOS (ICD 1489). The larynx group included cancers of vocal cord (ICD-1610), supra glottic larynx (ICD-1611), and larynx NOS cases (ICD-1619). During the study period, 635 of the male patients interviewed were diagnosed as being free from cancer, infectious disease (tuberculosis of lung and lymph nodes), and benign lesion (adenoma, fibroma, etc.), and these patients were classified as hospital control. The majority of the male controls whom we had considered for the study attended the hospital for complaints in the head and neck region and were later found to have no evidence of disease or any abnormality. The dietary practices were broadly classified as vegetarian and nonvegetarian diet. Those who have a vegetarian diet do not eat poultry products, fish, or meat.

In general, chewers consume pan, betel nut, lime, and tobacco with some spices and condiments, and smokers consume bidi (made by wrapping 0.2 g to 0.3 g of tobacco in tendu leaf), cigarette, chutta (a kind of cigar), hukka, and chilum (clay pipe). Bidi smoking is prevalent in all section of the population in the country. Cigarette smoking, though prevalent, is not as common as bidi smoking. Alcohol is locally brewed liquor mostly from palm trees (ethanol content: 40–60%). Statistical analysis is based on the unconditional logistic regression method and 95% confidence limits for the estimated odds ratio are obtained from the standard error of the estimates.

III. RESULTS

The general features of cancer patients and control are presented in Table I. There are 678 patients in the oropharynx group, 593 patients in the hypopharynx group, and 427 patients in the larynx group. Religious distribution of cancer patients and controls did not show much variation in relative frequencies, and hence this factor was not considered in the analysis. Among controls, 175 patients (27.6%) did not report any of the habits. In the cancer group, 46 patients (6.8%) in the oropharynx group, 56 patients in the hypopharynx group (9.4%), and 41 patients (9.6%) in the larynx group were free from the habits considered in the study. The habit of alcohol drinking was reported in 124 males (19.2%) in the control group. In the cancer group, there were 174 patients (25.7%) with the alcohol habit in the oropharynx group, 162 patients (27.3%) in the hypopharynx group, and 113 patients (26.5%) in the larynx group.

Alcohol drinking as a single habit was reported only by 2 males in the oropharynx group, 7 males each in the hypopharyngeal and laryngeal groups, and 10 males in the control group. In general, alcohol addicts also reported one of the other habits, like tobacco chewing or smoking, or both, and the independent risk due to alcohol could not be analyzed in our study. Among smokers, bidi smokers were common in both cases and controls, and the percentages varied between 63% in the control and 89% in the cancer group. Among smokers, 34% of males in the control group and 9 to 18% of males in the cancer group were cigarette smokers. The literacy level was high among the control group (71%) compared with the cancer group (55–64%).

Relative risk (RR) estimates for factors and tests of significance are shown in Table II. Cases and controls were stratified by three types of residence (Mumbai, Maharashtra, others) and four age groups (<35, 35–44, 45–54, 55+ years). Among the factors studied, smoking and alcohol drinking were shown to be significant risk factors in the three cancer groups. The chewing habit—in particular, tobacco chewing—did not emerge as a significant factor. Bidi smoking, a known risk factor, is also confirmed as a risk factor in our data. For bidi smokers, RR is 5.6 for oropharynx (confidence interval [CI]: 4.1–7.6), 2.6 for hypopharynx (CI: 2.0–3.5), and 2.3 for laryngeal (CI: 1.7–3.2) cancer. Cigarette smoking did not emerge as a significant risk factor for all the three groups in our study.

RR estimates and test of significance for frequency and duration of the habits are shown in Table III. The trend analysis was restricted to bidi smoking and alcohol drinking habits only. Bidi smokers who smoked 31 times and more per day had a 12-fold risk

TABLE I
General Features of Patients and Controls

	Controls	Oropharynx	Hypopharynx	Larynx
TOTALS	635	678	593	427
Number ICD-9 site				
1410 Base tongue		495	—	—
1453 Soft palate		57	—	—
1469 Oropharynx NOS		126	—	—
1480 Post Cricoid		—	29	—
1481 Pyriform		—	478	—
1489 Hypopharynx NOS		—	86	—
1610 Vocal cord		—	—	81
1611 Supra glottic		—	—	278
1619 Larynx NOS		—	—	68
Age group				
<35 years	139 (22)[a]	14 (2)[a]	25 (4)[a]	8 (2)[a]
35–44 years	175 (28)	84 (12)	68 (12)	36 (8)
45–54 years	156 (24)	216 (32)	174 (29)	140 (33)
55+ years	165 (26)	364 (54)	326 (55)	243 (57)
Avg. age ± SD	45.4 ± 12.9	54.3 ± 9.7	54.1 ± 10.6	54.9 ± 9.3
Residence				
Mumbai	386 (61)	269 (40)	222 (37)	159 (37)
Maharashtra	136 (21)	229 (34)	248 (42)	164 (38)
Others	111 (18)	180 (26)	123 (21)	104 (25)
Unknown	2 (—)	—	—	—
Religion				
Hindu Maharashtra	255 (40)	251 (37)	290 (49)	193 (45)
Hindu Gujarath	59 (9)	109 (16)	60 (10)	50 (12)
Sindhi	15 (3)	10 (2)	6 (1)	5 (1)
Hindu others	150 (24)	152 (22)	105 (18)	86 (20)
Muslim	104 (16)	113 (17)	99 (17)	65 (15)
Christian	28 (4)	26 (4)	17 (3)	13 (3)
Other religions	24 (4)	17 (2)	16 (2)	15 (4)

[a] Numbers within parentheses are percentages.

for oropharyngeal cancer, an 8-fold risk for hypopharyngeal cancer, and about a 4-fold risk for laryngeal cancer. Alcohol users also showed a 2-fold risk of pharyngeal and laryngeal cancers for drinking once a day. The trend analysis for alcohol habit was also significant. The dose-response relationship in terms of duration in years for bidi smokers and alcohol users was also found to be statistically significant in all three cancer groups.

RR estimates for literacy status and diet among three cancer groups and tests of significance are shown in Table IV. Illiterates had more than 50% excess risk for oropharyngeal and hypopharyngeal cancers only. For laryngeal cancer, literacy status did not seem to be a factor in our study. Nonvegetarian diet did not emerge as a significant factor in our study compared with vegetarian diet.

Unconditional logistic regression method was used to fit the data after adjusting for the four age groups and the three types of residence, and the results are presented in Table V. Bidi smoking and alcohol habit emerged as significant excess risk factors for all the three cancer groups. Illiteracy as a factor was established for cancer of oropharynx and hypopharynx. Diet, particularly nonvegetarian diet, seem to be a protective factor for cancer of oropharynx only, not for cancer of hypopharynx and larynx. Tobacco chewing emerged as a factor only in hypopharyngeal cancer, with a RR of 1.32 (CI: 1.01–1.73).

Data on cessation of smoking and chewing habits were collected for patients and controls. There were 28 patients who reported cessation of bidi smoking in the control group. Among the cancer group, 91 patients in the oropharynx, 60 patients in the hypophar-

TABLE II
RR Estimates for Chewers, Smokers, and Alcohol Users, and Tests of Significance[a]

		Oropharynx		Hypopharynx		Larynx	
Factors	Controls	Cases	RR	Cases	RR	Cases	RR
Chewers							
Non-chewers	382	434	1.0	330	1.0	230	1.0
Chewers	249	243	0.8 (0.6–1.01)[b]	256	1.1 (0.9–1.5)[b]	191	1.1 (0.82–1.47)[b]
Not recorded	4	1		7		6	
Chewing type							
Non-chewers	382	434	1.0	330	1.0	230	1.0
Tobacco chewers	233	219	0.7 (0.6–0.9)	242	1.1 (0.8–1.5)	179	1.1 (0.83–1.51)
Non-tobacco chewers	11	18	1.2 (0.5–3.1)	11	1.0 (0.4–2.8)	8	0.8 (0.25–2.75)
Others	5	6	0.7 (0.2–3.4)	3	0.6 (0.1–3.8)	4	0.8 (0.15–4.62)
Not recorded	4	1		7		6	
Smoking							
Nonsmokers	337	132	1.0	194	1.0	139	1.0
Smokers	294	545	4.1 (3.1–5.4)	392	2.0 (1.5–2.6)	282	2.0 (1.48–2.7)
Not recorded	4	1		7		6	
Smoking type							
Nonsmokers	337	132	1.0	194	1.0	139	1.0
Bidi	186	485	5.6 (4.1–7.6)	344	2.6 (2.0–3.5)	219	2.3 (1.7–3.2)
Cigarette	98	45	1.3 (0.8–2.2)	41	0.8 (0.5–1.4)	53	1.5 (0.9–2.4)
Bidi + cigarette	7	10	2.4 (0.7–8.4)	3	0.4 (0.1–2.5)	6	1.5 (0.4–6.0)
Other	3	5	2.4 (0.4–15.7)	4	2.7 (0.1–8.4)	4	2.2 (0.04–94.9)
Not recroded	4	1		7		6	
Alcohol							
Nonuser	509	503	1.0	424	1.0	308	1.0
Alcohol user	122	174	1.64 (1.2–2.3)	162	1.66 (1.2–2.3)	113	1.68 (1.20–2.43)
Not recorded	4	1		7		6	

[a] Stratified by four age groups and three types of residence.
[b] Figures in parentheses indicate the confidence interval.

ynx, and 49 patients in the larynx group reported to have stopped the habit. For those bidi smokers who stopped the habit for a period of 3 years or more, there was a significant reduction in risk of cancer in all three sites (data not shown).

IV. DISCUSSION

This is a retrospective unmatched case-control study using hospital controls. The interviewer bias was eliminated, as the patients were interviewed before the clinical examination. For a number of different reasons, not all patients with pharyngeal and laryngeal cancer who registered during the period could be interviewed. These are some of the limitations of the study which may or may not have affected the relative risk estimates. Previous studies from India did not analyze the effect of alcohol habit with head and neck cancer mainly due to social stigma associated with the habit and governmental ban on alcohol drink-

TABLE III
RR for Bidi Smoking and Use of Alcohol and according to Frequency per Day and Duration

		Oropharynx		Hypopharynx		Larynx	
Factors	Controls	No.	RR	No.	RR	No.	RR
Bidi							
Frequency							
Nonuser	445	193	1.0	242	1.0	203	1.0
1–10 times	77	188	4.3 (3.1–6.5)	126	2.1 (1.5–3.1)	93	1.8 (1.22–2.8)
11–20 times	52	124	4.9 (3.3–7.9)	81	2.5 (1.6–4.0)	38	1.4 (0.8–2.4)
21–30 times	53	141	4.7 (3.2–7.2)	112	3.5 (2.4–5.5)	76	2.5 (1.7–4.1)
31+ times	4	31	12.2 (3.8–42.4)	25	8.3 (2.3–26.0)	11	3.8 (0.9–14.1)
Not recorded	4	1		7		6	
Duration							
Nonuser	445	193	1.0	242	1.0	203	1.0
1–10 years	62	44	2.4 (1.5–4.1)	44	1.8 (1.1–3.1)	24	1.2 (0.7–2.3)
11–20 years	46	89	4.7 (3.4–8.6)	61	2.7 (1.8–4.9)	44	2.3 (1.4–4.3)
21–30 years	38	159	7.0 (4.5–11.4)	95	3.3 (2.2–5.7)	62	2.3 (1.4–4.1)
31+ years	40	192	5.2 (3.4–8.1)	144	3.0 (1.9–4.7)	88	2.0 (1.3–3.2)
Not recorded	4	1		7		6	
Alcohol							
Frequency							
Nonuser	509	503	1.0	424	1.0	308	1.0
Once	108	151	1.7 (1.3–2.4)	134	1.7 (1.2–2.3)	85	1.5 (1.0–2.2)
Twice	14	23	1.4 (0.6–3.4)	28	1.8 (0.8–4.2)	27	2.8 (1.4–7.5)
Not recorded	4	1		7		7	
Duration							
Nonuser	509	503	1.0	424	1.0	308	1.0
1–10 years	62	58	1.6 (1.04–2.7)	54	1.6 (1.0–2.5)	37	1.6 (0.9–2.7)
11–20 years	35	55	1.8 (1.1–3.2)	54	2.0 (1.2–3.5)	37	2.3 (1.4–4.5)
21–30 years	14	43	2.0 (1.1–4.3)	39	1.9 (0.9–3.9)	29	1.9 (0.9–4.1)
31+ years	11	18	0.9 (0.4–2.1)	15	0.95 (0.4–2.4)	10	0.6 (0.2–1.7)
Not recorded	4	1		7		6	

Note: Figures in parentheses show lower and upper confidence limit.

ing in all the states in India. Due to this, many of the studies carried out did not collect data on alcohol habit. Furthermore, women in India will not openly admit the habit of drinking alcohol. This is one of the reasons for restricting our data to males only for this study. The emergence of alcohol as an additional risk factor in our population for pharyngeal and laryngeal cancers is in conformity with the studies reported

TABLE IV
RR Estimates for Literacy and Diet with Confidence Interval and Tests of Significance after Adjusting for Age and Residence

Factor Site	Cases	Controls	RR	Confidence interval	*p* value
Literacy					
Oropharynx					
Literate	391	448	1.0		
Illiterate	286	183	1.56	1.21–2.06	<0.001
Not recorded	1	4			
Hypopharynx					
Literate	319	448	1.0		
Illiterate	267	183	1.62	1.24–2.14	<0.001
Not recorded	7	4			
Larynx					
Literate	267	448	1.0		
Illiterate	154	183	1.11	0.82–1.52	0.486
Not recorded	6	4			
Diet					
Oropharynx					
Vegetarian	231	148	1.0		
Nonvegetarian	446	483	0.77	0.58–1.03	0.065
Not recorded	1	4			
Hypopharynx					
Vegetarian	143	148	1.0		
Nonvegetarian	443	483	1.24	0.90–1.69	0.173
Not recorded	7	4			
Larynx					
Vegetarian	117	148	1.0		
Nonvegetarian	304	483	1.12	0.79–1.58	0.504
Not recorded	6	4			

from Western countries.[12–17] Compared with Western countries, the risk levels are very low in our population. Further studies are required to collect detailed data on alcohol according to types of alcohol and quantity consumed in our population.

Data reported in "Cancer Incidence in Five Continents, Vol. V"[10] for different populations and ethnic groups show that laryngeal cancer (ICD-161) incidence rates usually are higher than or almost equal to the rates for cancers of oropharynx (ICD-146) and hypopharynx (ICD-148) in both sexes. Even in India, where population-based registry data are available, incidence rates show a similar pattern. The reason for higher incidence of laryngeal cancer is not clear. Tobacco and alcohol are major risk factors for laryngeal cancer uniformly reported from the studies conducted in both developing and developed countries.[16,18] Among tobacco chewers and smokers, our study showed that bidi smokers are at a higher risk of about 5.6 times for oropharyngeal cancer, and the risk level decreased gradually for hypopharynx and larynx cancer. In our study, though alcohol has emerged as a risk factor for pharyngeal and laryngeal cancer, the risk level is about 2-fold only. Misclassification of primary site code when lesion with two adjacent sites is involved is also a possible explanation for the differences observed in incidence rate. It is not possible to explain from the study the reason for the high incidence of laryngeal cancer in our population compared with oropharyngeal and hypopharyngeal cancers.

In this study, nonvegetarian diet was not shown to be a risk factor for laryngeal and hypopharyngeal cancers, whereas it was found to be a risk factor for oral cancer.[3] In a case-control study of aerodigestive tract cancers, Notani and Jayant[2] assessed the role of dietary items such as fruits, vegetables, beverages, dairy products, meat, fish, and poultry products. They also did not find excess risk due to the consumption of meat and poultry products, which are part of a nonvegetarian diet; also, in this study consumption of fish

TABLE V
Unconditional Logistic Regression Model Using Five Factors for Three Sites

Site Factor	RR	Confidence interval	*p* value
Oropharynx			
Bidi (1 = yes; 0 = no)	4.69	3.64–6.29	<0.001
Alcohol (1 = yes; 0 = no)	1.53	1.04–2.03	<0.001
Illiteracy (1 = yes; 0 = no)	1.45	1.09–1.94	0.011
Nonvegetarian (1 = yes; 0 = no)	0.67	0.45–0.85	0.004
Tobacco chewing (1 = yes; 0 = no)	0.97	0.67–1.19	>0.05
Hypopharynx			
Bidi (1 = yes; 0 = no)	2.79	2.13–3.65	<0.001
Alcohol (1 = yes; 0 = no)	1.54	1.12–2.11	0.008
Illiteracy (1 = yes; 0 = no)	1.38	1.05–1.82	0.018
Nonvegetarian (1 = yes; 0 = no)	1.02	0.74–1.41	0.899
Tobacco chewing (1 = yes; 0 = no)	1.32	1.01–1.73	0.041
Larynx			
Bidi (1 = yes; 0 = no)	2.11	1.58–2.82	<0.001
Alcohol (1 = yes; 0 = no)	1.64	1.16–2.31	0.005
Illiteracy (1 = yes; 0 = no)	1.02	0.76–1.38	0.911
Nonvegetarian (1 = yes; 0 = no)	0.97	0.69–1.36	0.852
Tobacco chewing (1 = yes; 0 = no)	1.24	0.93–1.66	0.143

was shown to be a protective factor, whereas Winn and colleagues[19] did not find it to be a significant protective factor. Nor, however, did Winn et al. find significant association of pharyngeal cancer with meat and fish intake.[19] Further, use of red chilli powder of more than 75 g/cu/month has been shown to increase the risk of cancer. Salted meat consumption (fresh) was associated with increased risk of laryngeal cancer,[18] whereas consumption of preserved meat reduced the risk of laryngeal cancer.[15] Daily consumption of vegetables, fruits, and dairy products have been shown to be protective factors for pharyngeal cancers including nasopharynx.[2,15,20] Glutathione, a tripeptide found in a variety of foods, especially derived from fruit and vegetables commonly consumed raw, was associated with reduced cancer risk.[21] Unless patients and controls are assessed for each and every item of diet, it will be difficult to quantitate the risk of dietary items.

Maté, a tea-like infusion of the herb *Ilex paraguariensis*, commonly consumed in South America has been shown to be associated with laryngeal cancer.[22]

Some occupational exposures have emerged as one of the risk factor for pharyngeal and laryngeal cancer. An excess risk of laryngeal cancer associated with exposure to machining fluids for automobile workers[23] as well as exposure to asbestos for asbestos workers[24] has been reported. An increased risk of pharyngeal cancer was found for construction workers exposed to cutting oils, iron dust, asbestos cement, cement, and coal/tar products.[25]

Environmental factors such as EBV and diet, and other genetic factors are also believed to increase the risk of tongue, oral, and nasopharyngeal cancer among the circumpolar Inuit population (including that of Alaska, Canada, and Greenland).[26]

The emergence of illiteracy as a high risk factor (38–45% excess risk) for oropharyngeal and hypopharyngeal cancer after adjusting for other risk factors in our study just points to the possibility of differences in socioeconomic conditions, poor oral hygiene, and lifestyle. An earlier case-control study also brought out the significance of illiteracy as a factor for oral cancer.[3] The preventive measures in a society with considerable variation in literacy status need to be focused in an appropriate manner, and different strategies for cancer control need to evolve.

In conclusion, alcohol has been shown as a risk factor for oral, pharyngeal, and laryngeal cancers in Mumbai. In order to prevent head and neck cancer, particularly in a country like India, the government should propagate the ill effect of alcohol habit along with tobacco usage and initiate steps to ban

advertising of alcohol in the press and other visual media.

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Supplement to

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Oxaliplatin: A New Option for the Treatment of Colorectal Cancer

Esteban Cvitkovic, MD, and Stephen G. Chaney, PhD, *Guest Editors*

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Seminars in Oncology

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A Historical Perspective on Oxaliplatin: Rethinking the Role of Platinum Compounds and Learning From Near Misses

Esteban Cvitkovic

OF THE MANY thousands of platinum compounds synthesized over the last 30 years (not to mention other metal compound hopefuls), only a few dozen have reached preclinical or early clinical development. Of these, until recently, only cisplatin and carboplatin were available. Both have similar clinical properties, and carboplatin was approved solely on its superior safety profile. Additionally, the diaminocyclohexane (DACH) platinum family of compounds was shown, in the early 1970s, to be non–cross-resistant with cisplatin and to have a different preclinical activity profile. Most of this interest was US based and centered around a few DACH platinum research mavens, with Stephen Chaney, the present co-editor, being the current *chef-de-file*. The most promising DACH platinum, tetraplatin (ormaplatin), had a negative phase I experience characterized by severe neurologic toxicity with disabling characteristics, which considerably dampened the enthusiasm for DACH platinums in the United States.

The almost-forgotten ugly duckling in the DACH family was oxaliplatin (oxalato[*trans-l*-1,2-diaminocyclohexane] platinum). In the mid-1970s, Professor Kidani described the relationship between the stereoisomeric specificity of DACH platinum compounds binding to DNA and cytotoxicity,[1] but it was not until 12 years later, in the late 1980s, that Professor Georges Mathé had the foresight to bring oxaliplatin to the clinic.[2] This first and unorthodox phase I trial evidenced both the activity and the exceptionally safe toxicity profile of oxaliplatin, which was devoid of renal, hematologic, and/or auditory toxicity. Whereas rapid bolus administration and accelerated intrapatient escalation did lead to underestimation of the recommended dose of oxaliplatin, Extra and colleagues[3] gave a more accurate definition of its triweekly short intravenous dosage, while Dr Lévi[4] kept the flame alive on a drug that held no one else's interest.

Oxaliplatin was developed mainly within the Paul Brousse Hospital by the only group that had both experience and belief in the positive therapeutic possibilities of this agent. While J.L. Misset[5] continued with single-agent and combination experiences in other disease indications, Lévi and colleagues[4] treated several hundred patients with colorectal cancer in an extensive chronotherapy delivery clinical research experience, their main preclinical and clinical research interest. The excellent results reported in patients with advanced colorectal cancer (ACRC) by the chronotherapy experts were emphasized more in the context of a specific pharmacodynamic antitumoral advantage of the delivery modality than as a specific contribution from oxaliplatin.

A standard single-agent phase II program was launched in a variety of solid tumors, with oxaliplatin given according to the currently recommended dose of 130 mg/m^2 in a 2-hour intravenous infusion every 3 weeks, confirming its safety. Meanwhile, three concomitant series of events renewed interest in the essential features of the differential pharmacodynamic specificity of oxaliplatin and in the treatment of patients with colorectal cancer:

1. A. de Gramont,[6] whose team's interest is the clinical optimization of a hybrid/bolus sequence of fortnightly 48-hour delivery of high-dose infusional 5-fluorouracil/folinic acid (5-FU/FA) schedules, added oxaliplatin to his LV5-FU2 (leucovorin/5-fluoro-

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uracil) schedule and confirmed Lévi's observation that the oxaliplatin/5-FU combination was active in strictly defined 5-FU–refractory patients.[4] This convinced interested observers that such efficacy is independent of chronotherapy delivery schedules.

2. Preclinical studies by Rixe et al[7] and Raymond et al[8] confirmed the observations of previous generations of DACH platinum authorities while demonstrating that the mechanism of action of oxaliplatin is different from that of conventional platinum agents and that it acts synergistically in combination with 5-FU and other agents. Until then, the US preclinical research interest in DACH platinums had been mostly confined to teams at M.D. Anderson Cancer Center (Houston, TX), National Cancer Institute (Bethesda, MD), Roswell Park Cancer Institute (Buffalo, NY), and the University of North Carolina, Chapel Hill. But even after the development of tetraplatin was curtailed, Chaney's team continued to study the molecular properties specific to DACH platinums.
3. The single-agent phase II trials in 5-FU–refractory patients with ACRC demonstrated the specific antitumor activity of oxaliplatin for this disease. New single-agent data in previously untreated patients have since shown the same range of objective response rates as with 5-FU as a single agent.

A wider clinical exposure to oxaliplatin-based ACRC treatment led quickly, through prescriber and patient education, to an understanding of the pattern, rate, severity, and reversibility (not a feature of cisplatin neurotoxicity) of oxaliplatin neurosensory toxicity. Consequently, oxaliplatin withstood rigorous tests of convincing and relevant evidence, time, and negative serendipity. Marketing approval was granted in France in March 1996 for patients with ACRC who had been previously treated and in early 1998 for first-line treatment. European, US, and worldwide filings have either been done or are forthcoming. Data from thousands of treated patients have been reported, including the results of two controlled phase III trials in previously untreated patients with ACRC comparing oxaliplatin–5-FU/FA and 5-FU/FA. The trial by Giacchetti and colleagues[9] shows a nearly threefold increase in response rate and a 3-month extension in time to progression, favoring the oxaliplatin arm. The second multicentric trial of 420 patients, chaired by A. de Gramont, completed accrual in mid-1997; results will be available shortly.[10]

I have personally led the analysis of hundreds of patients with ACRC treated in compassionate-use, extended-access programs. The results in such heavily pretreated, unrestricted eligibility cohorts seem relatively independent of the 5-FU or oxaliplatin delivery modality; the biweekly delivery of oxaliplatin/5-FU ± FA appears at least as active and as safe as the currently recommended triweekly schedule.

The current interest in oxaliplatin is evidenced by the plethora of ongoing and planned clinical studies. The recently defined differences between cisplatin and oxaliplatin, in replicative bypass and mismatch repair-dependent cytotoxicity, have given a molecular basis for the understanding of their different profiles of activity. The current definition of anticancer agent groups proposed recently by the National Cancer Institute from analyses of its in vitro cytotoxicity screening program relies both on the biochemical targets and on the mechanisms of resistance operational in the different cell types. In this classification, the DACH family has been identified as a completely new group of anticancer agents. We are thus reasonably comforted by its apparent clinical specificity, which will open new indications for platinum compounds. This may eventually lead to sharing, complementing, or even replacing cisplatin and carboplatin in a host of specific clinical settings.

What constitutes a major new anticancer agent? In my opinion, the prerequisites for such a role are based on four premises:

1. It must have antitumoral activity in the clinical setting in which few or no previous therapeutic options existed.
2. It is the backbone of combination schedules in which clinical efficacy/additivity/synergy are proven within a safe and reliable prescription possibility.
3. Its incorporation in the therapeutic armamentarium does improve time-related parameters of treatment outcome.
4. Most importantly, it changes, merely through clinical experience, the physician's therapeutic options algorithms, helping to individualize and optimize patient treatment.

All these points are characteristic of the clin-

ical experience with oxaliplatin for colorectal cancer treatment. The most telling piece of information is probably the rate of secondary hepatic resections (approximately one third of patients) performed by those teams of surgeons most experienced in its use. The fact that the possibility of long-term survival is acknowledged by experienced physicians and that the results obtained by the Bismuth team[11] have generated many followers reflects the change in physicians' thinking.

Until very recently, second-line treatment of patients with colorectal cancer was a limited therapeutic option, confined mostly to locoregional (intra-arterial) or infusional 5-FU treatment of 5-FU failures. The availability of both oxaliplatin and CPT-11, and the incoming wave of new thymidylate synthase inhibitors (oral administration now appears both feasible and reliably active), multiplies the associative possibilities of these three different agents and will expand the palliative treatment of colorectal cancer.

Oxaliplatin, both a new and a major anticancer agent for the treatment of colorectal cancer, has arrived. It is now up to us, the medical oncologists, to do the best. In that sense I cannot help being optimistic, but with a warning note.

In the 1970s, anthracyclines and tamoxifen became available for breast cancer treatment, simultaneously with the availability of reliable biochemical determinants of treatment outcome: the tumoral hormone receptors. Such coincidental circumstances, coupled with the proof of adjuvant treatment efficacy, led to a revolution in therapeutic practice. In the breast cancer arena, the trickling down to positive changes in clinical benefit took over two decades.

The treatment of colorectal cancer by pharmacologic means is at the same crossroads as was breast cancer 25 years ago. New and putative treatment-dependent prognostic/predictive biological parameters of therapeutic outcome are rapidly being identified, including p53 functionality, thymidylate expression, and mismatch repair defects. Learning from the past means not repeating mistakes. We should not spend two decades trying to improve the treatment of colorectal cancer when an opportunity such as oxaliplatin exists.

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Oxaliplatin: Mechanism of Action and Antineoplastic Activity

Eric Raymond, Sandrine Faivre, Jan M. Woynarowski, and Stepnen G. Chaney

Oxaliplatin, a platinum-based chemotherapeutic agent with a 1,2-diaminocyclohexane (DACH) carrier ligand, has shown in vitro and in vivo efficacy against many tumor cell lines, including some that are resistant to cisplatin and carboplatin. The retention of the bulky DACH ring by activated oxaliplatin is thought to result in the formation of platinum-DNA adducts, which appear to be more effective at blocking DNA replication and are more cytotoxic than adducts formed from cisplatin. Studies by the National Cancer Institute (NCI) have suggested that oxaliplatin has a spectrum of activity different from that of either cisplatin or carboplatin, suggesting that it has different molecular targets and/or mechanisms of resistance. Oxaliplatin has been demonstrated to differ in some mechanisms associated with the development of cisplatin resistance. Compared with cisplatin-conditioned cells, deficiencies in mismatch repair (MMR) and increases in replicative bypass, which appear to contribute to cisplatin resistance, have not been shown to induce a similar resistance to oxaliplatin. A decreased likelihood of resistance development makes oxaliplatin a good candidate for first-line therapy. Studies also demonstrate additive and/or synergistic activity with a number of other compounds, however, suggesting the possible use of oxaliplatin in combination therapies.

Semin Oncol 25(suppl 5):4–12.

EVEN before cisplatin (*cis*-diamminedichloroplatinum [CDDP]) was successfully introduced as an antitumor agent[1,2] in the 1970s, a search for analogues with a better toxicity profile and an improved spectrum of activity was actively pursued. Over 25 years, a large number of platinum derivatives (several thousand) were synthesized and investigated. Among these, compounds containing a 1,2-diaminocyclohexane (DACH) carrier ligand demonstrated antitumor activity in cell lines with acquired cisplatin resistance.[3,4] This aspect was important because the occurrence or development of intrinsic or acquired resistance is a major clinical problem associated with platinum-based chemotherapy, with cisplatin and carboplatin sharing cross-resistance in most tumor types. Among the platinum derivatives, compounds bearing the DACH carrier ligand are particularly promising because this class lacks the nephrotoxicity of cisplatin and the myelosuppression of carboplatin, is effective in cell lines with acquired cisplatin resistance, and appears to be clinically active in tumor types that are intrinsically resistant to cisplatin. Lack of cross-resistance with cisplatin implies a different mechanism of antitumor activity or resistance, as demonstrated in a National Cancer Institute cytotoxicity screening study.[5,6]

Among the platinum derivatives bearing the DACH carrier ligand, compounds such as malonatoplatinum and tetraplatin reached the early clinical trial stage; however, therapeutic index, toxicity, and galenic issues compromised their further development. Only oxaliplatin ([SP-4-2-(1*R*-*trans*)]-(1,2-cyclohexanediamine-*N*,*N*′)[ethanedioato(2-)-*O*,*O*′] platinum), one of the most active DACH-platinum derivatives against cisplatin-resistant murine L1210 leukemia cells[7] and various human cancer cell lines,[5] has been successfully developed, and it has already been registered for the treatment of patients with advanced colorectal cancer in France, Argentina, and some other countries.

The DACH-platinum complex of oxaliplatin can exist as three isomeric conformations: *trans-l*(R,R), *trans-d*(S,S), and *cis*(R,S). Kidani and colleagues[8,9] first suggested that the stereochemical conformation of the DACH carrier ligand may affect its interaction with DNA and influence cytotoxicity. The *trans-l*(R,R) isomer of oxaliplatin appears to be the most effective of the three conformers against cisplatin-sensitive and cisplatin-resistant cell lines in vitro.[10] Consequently, this conformer was selected for further preclinical development on the basis of the physicochemical data currently available.

BIOTRANSFORMATION AND MECHANISM OF ACTION

Preclinical studies with the malonate derivative of 1,2-DACH-platinum, a compound expected to

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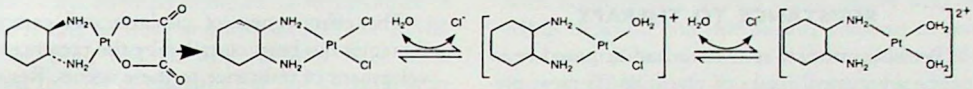
■ Oxaliplatin Biotransformation:

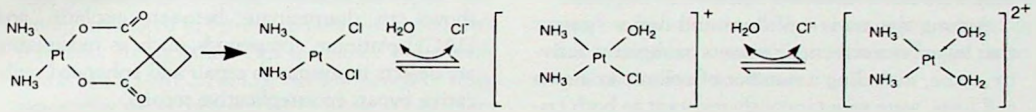
Oxaliplatin → DACH-Pt-Cl_2 → DACH-Pt-Cl_2H_2C → DACH-Pt-Diaqua



oxaliplatin $PtCl_2$(dach) $[Pt(H_2O)(Cl)(dach)]^+$ $[Pt(H_2O)_2(dach)]^{2+}$

■ Carboplatin / Cisplatin Biotransformation:

Carboplatin → Cisplatin → cis-Diammine-Pt-H_2O → cis-Diammine-Pt-Diaqua



carboplatin cisplatin $[Pt(H_2O)(Cl)(NH_3)_2]^+$ $[Pt(H_2O)_2(NH_3)_2]^{2+}$

Fig 1. Biotransformations of oxaliplatin and cisplatin.

display chemical properties similar to those of oxaliplatin, have suggested that weak nucleophiles such as blood bicarbonate or intracellular dihydrogen phosphate can displace the oxalate group in the complex.[11] The resulting intermediates are unstable and readily hydrolyzed to diaquated 1,2-DACH-platinum. Depending on the immediate environment, this species can be rapidly interconverted to monoaqua-1,2-DACH-monochloroplatinum or 1,2-DACH-platinum dichloride. In a high-chloride environment such as blood, the latter prevails. Within the cell, where the chloride concentration is lower, the aquated species predominates. These compounds are analogous to the reactive aquated platinum species that result from cisplatin and carboplatin activation.[12] However, whereas carboplatin and cisplatin have a common *cis*-diammine intermediate, the biotransformation products of oxaliplatin retain the DACH carrier ligand in their reactive entities (Fig 1). This suggests the possibility that the 1,2-DACH ligand could have major effects on the rate of reaction of the active complex with DNA, the types of platinum-DNA adducts formed, or the biologic properties of the resulting adducts. Previous studies have shown that the 1,2-DACH carrier ligand does not affect the rate of reaction of the active platinum complex with DNA or with the types of platinum-DNA adducts formed.[13] However, it does affect the rate of monoadduct to diadduct conversion[13] and the ability of cells to tolerate unrepaired platinum-DNA adducts.[14,15] The effect of the 1,2-DACH ligand on the ability of cells to tolerate platinum-DNA adducts appears to be primarily responsible for differentiating the antitumor effects of oxaliplatin from those of carboplatin or cisplatin.

Although the precise mechanism of oxaliplatin remains unclear, platinum compounds in general are thought to exert their cytotoxic effects through the formation of various types of DNA lesions. While oxaliplatin appears to form the same type of lesions as cisplatin[16,17] at the same sites on the DNA,[17] DACH-platinum adducts formed by oxaliplatin are more effective at inhibiting DNA synthesis[17,18] and generally are more cytotoxic than *cis*-diammine-platinum adducts formed from cisplatin and carboplatin.[5,15,17]

Computer modeling of oxaliplatin-(GpG)-DNA adducts in a DNA dodecamer has predicted that the bulkier DACH group of oxaliplatin projects into the major groove. Damage recognition proteins such as the mismatch repair (MMR) enzyme complex may be prevented from binding to

oxaliplatin adducts because of the steric hindrance of the DACH ring.[19] Additionally, DNA replication may be adversely affected by the bulky oxaliplatin adducts.

RESISTANCE TO THERAPY

Because intrinsic resistance and acquired resistance are critical issues of platinum therapy, preclinical studies with human cancer cell lines have tended to evaluate the antineoplastic activity of oxaliplatin in the context of prior resistance to cisplatin or carboplatin, or both. In the course of these studies, however, it was demonstrated that in some instances, oxaliplatin was active in tumors that were not considered sensitive to cisplatin.[5,20]

Among the many cell lines and tumor systems that have been screened to assess oxaliplatin activity, some, including a number of colon carcinoma cell lines, were spontaneously resistant to both cisplatin and carboplatin. Others were subclones of cell lines sensitive to cisplatin, such as the ovarian cancer cell line A2780, but had developed resistance by progressive selection after extensive exposure to platinum. The determination of the efficacy of oxaliplatin in cells with intrinsic or acquired resistance to cisplatin was prompted by the realization that such resistance was probably due to entirely different molecular mechanisms.

Mechanisms of Resistance to Platinum Compounds

The effectiveness of cisplatin and carboplatin therapies has been curtailed by the presence or development of resistance to these agents. Resistance to cisplatin and carboplatin can result from one or several biomolecular conditions in the target cells.[21] Resistance to platinum agents has been attributed to decreased drug accumulation, drug inactivation, enhanced tolerance to platinum-DNA adducts, or enhanced DNA repair[22] (Fig 2). However, the only resistance mechanisms that have reproducibly been shown to discriminate between cisplatin and DACH-platinum compounds, such as oxaliplatin, are defects in mismatch repair and enhanced replicative bypass (postreplicative repair).

Mismatch Repair and Resistance

Recent studies suggest that alterations in MMR activity may confer intrinsic resistance to cisplatin or carboplatin. To date, six genes (*hMLH1*, *hMLH2*, *hPMS2*, *hMSH2*, *hMSH3*, and *hMSH6*)

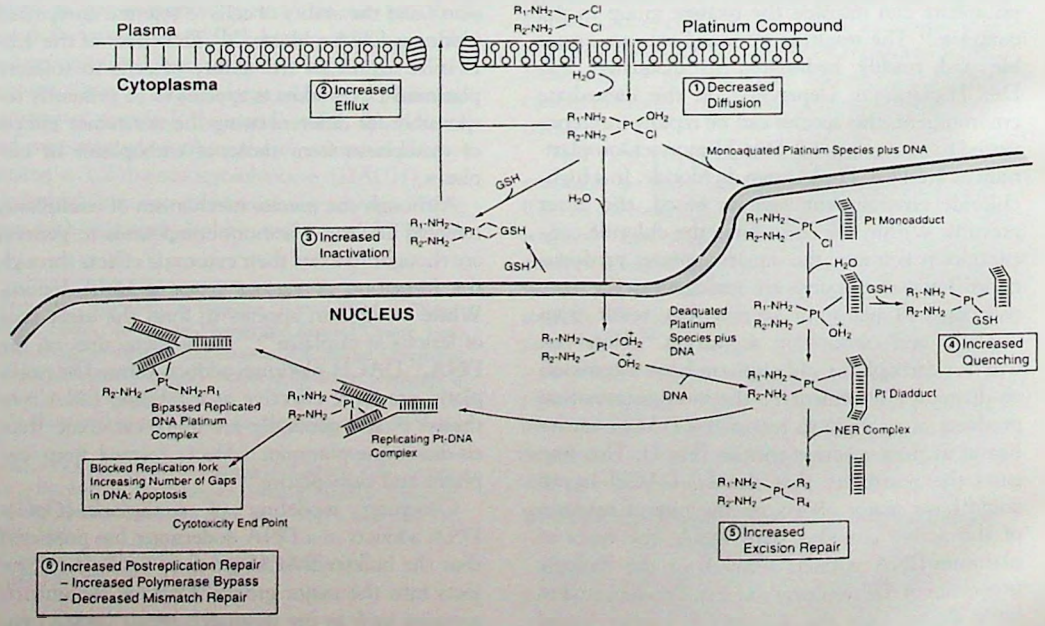


Fig 2. Platinum cytotoxicity and mechanisms of resistance.

have been identified as related to the MMR mechanism. When conventional mismatch occurs, the mismatch recognition complex hMutSα (a heterodimer of *hMSH2* and *hMSH6*) binds to the mismatch and primes the MMR system for recruitment of the hMutLα complex (a heterodimer of *hMLH1* and *hPMS2*) and initiation of the MMR system. Both hMSH2 and hMutSα have been shown to bind to cisplatin but not to oxaliplatin DNA adducts. Furthermore, defects in hMLH1, hMSH2, and PMS2 have been shown to result in cisplatin resistance but do not alter the sensitivity to oxaliplatin.[14,18,23-25]

Recent data have shown that the MMR-binding protein hMLH1 may be absent from cisplatin-resistant ovarian cancer cells.[26] Mismatch repair deficiency evaluated in vitro is usually associated with resistance to cisplatin. This resistance is generally minimal (1.5- to 2.5-fold), but low levels of resistance may nevertheless lead to clinical treatment failure. One current hypothesis concerning the significance of this finding proposes that in cisplatin-sensitive cells, hMutSα may act as a lesion marker and that binding of the MMR complex to a DNA adduct leads to continuous "futile" cycles of excision and resynthesis of the strand opposite the lesion, presumably to correct the mismatch. Instead, the recurring nature of such cycles may generate many gaps and strand breaks, leading to apoptotic cell death.[26] In resistant cells, the absence of components of either the hMutSα or hMutLα complex allows the cancer cell to replicate the damaged DNA with no attempt to repair the mismatch. The development of resistance attributable to a deficiency in an MMR protein also leads to microsatellite DNA instability, loss of p53-dependent cell cycle arrest function, and a reduced ability to engage in apoptosis.[27]

Several studies have demonstrated the effectiveness of oxaliplatin using models of MMR deficiency. Athymic nude mice with MMR-proficient grafts responded significantly better to cisplatin therapy than did mice with MMR-deficient grafts. However, both groups responded equally well to oxaliplatin.[28] Studies have also shown that colon carcinoma cell lines defective in either *hMLH1* or *hMSH2* display significant resistance to cisplatin but little or no resistance to oxaliplatin.[29] Furthermore, both *hMSH2* and the hMutSα complex have been shown to recognize cisplatin, but not oxaliplatin, diadducts with DNA.[29,30]

The current data indicate that loss of MMR is a contributor to intrinsic resistance to cisplatin, but not oxaliplatin. The relationship of MMR to intrinsic platinum resistance and to oxaliplatin toxicity may be especially relevant for patients with nonpolyposis familial colon cancer who are MMR-deficient and intrinsically resistant to conventional platinum therapies.[31] In addition, defects in MMR have also been reported in 5% to 20% of a wide variety of sporadic human tumors, including colorectal, ovarian, and breast, among others.[32-35] Further evidence suggests that cisplatin treatment may produce selective pressure for the survival of MMR-deficient cells, implying a role for oxaliplatin in cisplatin-acquired resistance.[25-32,36] Thus, the currently available evidence suggests that oxaliplatin may offer a therapeutic advantage for a variety of tumors with either intrinsic or acquired cisplatin resistance.

Replicative Bypass and Resistance

Additional factors may facilitate resistance to therapy and enhance the survival of cancer cells. For instance, enhanced replicative bypass (the ability of the replication complex to synthesize DNA past the site of DNA damage) of cisplatin-(GpG)-DNA adducts has been demonstrated in cisplatin-resistant murine L1210 cells[14] and human ovarian carcinoma cell lines.[18,37] In cisplatin-resistant human ovarian carcinoma cell lines, a twofold to sixfold enhanced replicative bypass of cisplatin adducts was observed; however, no difference in replicative bypass of oxaliplatin adducts was observed between the cisplatin-sensitive and cisplatin-resistant cell lines.[37] In addition, oxaliplatin adducts caused greater inhibition of DNA chain elongation than did cisplatin adducts in both cisplatin-sensitive and cisplatin-resistant cell lines. This suggests a DACH carrier ligand effect on the ability of the replication complex to bypass the platinum adduct. The precise molecular interactions involved in such a mechanism are not fully understood, but recent studies suggest that MMR complexes can have an important role in preventing the bypass process in some cell lines. Mismatch repair-deficient cell lines displayed a threefold to sevenfold higher incidence of replicative bypass of cisplatin adducts than MMR-proficient cell lines, while MMR status had no effect on the bypass of oxaliplatin adducts.[37] However, enhanced replicative bypass has also been seen in

Table 1. Median Concentration Inhibiting Proliferation by 50% (IC_{50}) In Various Murine and Human Tumor Cell Lines

Tumor Type	IC_{50} (μmol/L) Cisplatin	Oxaliplatin
Murine leukemia (L1210)*	0.80	0.41
Murine leukemia (P388)*	0.67	0.97
Human colon carcinoma (HT-29)†	20.4	0.97
Human ovarian carcinoma (A2780)†	0.76	0.17
Human breast carcinoma (MCF-7)‡	4.20	0.30

* Kraker and Moore.[49]
† Pendyala and Creaven.[50]
‡ Silvestro et al.[20]

MMR-proficient cell lines with acquired cisplatin resistance,[18] suggesting that alterations in either the replication complex or the MMR complex can lead to enhanced replicative bypass, which is selective for cisplatin adducts and is associated with acquired cisplatin resistance.

The current data demonstrate that both the alteration of the MMR process and replicative bypass of DNA adducts contribute to cisplatin resistance in ovarian cancer cell lines, but that such resistance can be overcome by a platinum agent with a bulky carrier group, such as oxaliplatin, that can make bypass more difficult and can prevent the binding of the MMR complex. While further investigation of other mechanisms is warranted, of all the known putative mechanisms of resistance to cisplatin, only defective MMR and enhanced replicative bypass of DNA adducts have been shown to adequately explain the non–cross-resistance with oxaliplatin at present.

PRECLINICAL EFFICACY

In Vitro Studies

Oxaliplatin has shown antiproliferative activity equivalent to or higher than that of cisplatin against both murine (L1210; P388) and human cancer cell lines, including, among others, HT29 colon carcinoma,[20] HEC59 colon carcinoma,[29] ovarian carcinoma cell line A2780, epidermal KB cells, breast MCF-7 cells, germ cell cancer cell lines,[18] and neuroblastoma cell lines[25] (Table 1).

A key study investigating the sensitivity of two cisplatin-resistant cell lines from the National Cancer Institute human cancer cell line panel—a clone of ovarian cancer A2780 and the epithelial KB 3-1 cell line (an HeLa subclone)—demonstrated that both clones were approximately 10-fold more resistant to cisplatin or carboplatin than to oxaliplatin[5] (Table 2). These data highlighted the activity of DACH-platinum compounds such as oxaliplatin against cisplatin-resistant cell lines and suggested that their mechanism of action differs from that of cisplatin or carboplatin. In the cisplatin-resistant non–small cell lung cancer subclones PC-9-CDDP and PC-14-CDDP, whereas oxaliplatin was somewhat less effective than cisplatin in the parental clone, the cisplatin-resistant clones were less resistant to oxaliplatin than to cisplatin[38] (Table 2). In the nonseminomatous germ cell cancer cell lines with either acquired (H12DDP clone) or intrinsic (1777Nrp Cl-A clone) intermediate levels of resistance to cisplatin, oxaliplatin was significantly more cytotoxic than cisplatin.[24]

Oxaliplatin also exerts potent in vitro cytotoxic activity against a large variety of human tumor colony-forming units isolated from patients. In

Table 2. Cytotoxicity to Platinum-Sensitive Cells and Magnitude of Resistance in Platinum-Resistant Cells Obtained With Three Drugs in Various Human Cancer Cell Lines

	Ovarian Cancer		Epithelial HeLa Subclone		Non–Small Cell Lung Cancer	
Antineoplastic Agent	A2780(1A9) CDDP-Sensitive, IC_{50} (μmol/L)	A2780-E80 CDDP-Resistant (Fold Resistance)	KB 3-1 CDDP-Sensitive, IC_{50} (μmol/L)	KB CP(20) CDDP-Resistant (Fold Resistance)	PC-14 CDDP-Sensitive, IC_{50} (μmol/L)	PC-14–CDDP CDDP-Resistant (Fold Resistance)
Cisplatin	0.21 ± 0.05	92	0.75 ± 0.38	78	2.7 ± 1.1	7.7
Carboplatin	0.35 ± 0.13	64	1.65 ± 0.88	57	21.1 ± 3.4	3.5
Oxaliplatin	0.12 ± 0.07	4.7	0.39 ± 0.22	2.7	6.1 ± 1.6	2.3

Data from Rixe et al[5] and Fukuda et al.[38]

Table 3. Oxaliplatin Concentration Dependence and Response Rates of Colony-Forming Units From Patients With Various Tumors in a Clonogenic Assay

	Clonogenic Response (%)			
Oxaliplatin (mg/mL)	0.5	5.0	10.0	50.0
1-hr exposure	9/116 (8)	18/115 (16)	38/103 (37)	7/13 (54)
14-d exposure	10/121 (8)	37/121 (31)	57/106 (54)	15/15 (100)

vitro responses have been observed in colon cancer; non–small cell lung, gastric, and ovarian cancers; and in a limited number of melanoma, renal cell carcinoma, and sarcoma specimens commonly considered highly resistant to conventional anticancer agents. Responses were dependent on length of exposure and oxaliplatin concentration (Table 3); additionally, significant responses were observed in clones resistant to a variety of conventional chemotherapeutic agents.[39]

It is important to keep in mind, however, that DACH-platinum complexes are clearly not effective in all cisplatin-resistant cell lines. For instance, oxaliplatin was less effective than cisplatin in the human ovarian cancer cell line OVCAR3, which is intrinsically resistant to cisplatin.[40] Additionally, moderate resistance to cisplatin and carboplatin, together with high resistance to DACH-platinum compounds, has been reported in some clones, especially those selected for resistance to DACH-platinum compounds (P6).[41,42]

In Vivo Models

The potent antitumor activity of oxaliplatin was first demonstrated in mice with L1210 or P388 leukemia (Table 4). In these initial studies, mice treated with oxaliplatin survived two to three times longer than control mice.[43,44] In addition, mice with L1210 leukemia treated with oxaliplatin had a higher number of cures than did mice treated with cisplatin. Subsequently, Mathé et al[44] also demonstrated potent oxaliplatin activity against L1210 (Table 4). Additionally, they showed that oxaliplatin treatment prolonged survival in mice with AkR leukemia and provided cure rates of over 50% in rodents infected with LGC lymphoma. In this series of experiments, Mathé et al[44] failed to demonstrate any effect of either cisplatin or oxaliplatin against grafts of glioma 26, B16 melanoma, or Lewis lung carcinoma. However, Tashiro et al,[7] using higher levels of oxaliplatin, were able to demonstrate a significant prolongation of survival in rodents grafted subcutaneously with a variety

Table 4. Antineoplastic Properties of Oxaliplatin Versus Cisplatin in Rodents

Murine Cell Type	Study	Cisplatin Dose (mg/kg)	Survival Treated/Control (%) (Other Observations)	Oxaliplatin Dose (mg/kg)	Survival Treated/Control (%) (Other Observations)
Hematologic tumors					
L1210 leukemia	Tashiro et al[7]	6.25	249	12.5	>308
L1210/CDDP-resistant	Tashiro et al[7]	6.25	107	6.25	>726
P388 leukemia	Noji et al[51]	3.12	230	12.5	231
	Tashiro et al[7]	6.25	237	12.5	221
L40 AkR leukemia	Mathé et al[44]	5	194	7.5	177
LGC lymphoma	Mathé et al[44]	5	Not active	5	>50% Cured
Solid tumors					
Fibrosarcoma M 5076	Tashiro et al[7]	5	211	10	358
Colon 26	Tashiro et al[7]	6.25	322	12.5	143
Colon 38	Tashiro et al[7]	10	153	10	153
MA16-C mammary	Mathé et al[45]	5	Not active	7.5	206

of solid tumors, including Lewis lung, colon, and fibrosarcoma (Table 4). In these experiments, the antineoplastic efficacy of oxaliplatin was comparable to that of cisplatin against P388 leukemia, B16 melanoma, and colon 38. Oxaliplatin was superior to cisplatin against L1210 leukemia, and fibrosarcoma M5067, and was significant against a clone of cisplatin-resistant L1210, prolonging rodent survival over sevenfold compared with the cisplatin-treated control.[7] In addition, a subsequent study by Mathé et al[45] was able to show good activity in MA16-C mammary carcinoma, while cisplatin was inactive.

Combination With Other Agents

Although the range of its preclinical interaction or sequence specificity in combination with other antineoplastic drugs has not been fully identified, oxaliplatin has demonstrated in vitro or in vivo additive or synergistic cytotoxic properties with most agents tested to date (Table 5), including fluoropyrimidines (5-fluorouracil [5-FU]), thymidylate synthase inhibitors (AG337), topoisomerase I inhibitors (CPT-11; SN-38), a microtubule inhibitor (paclitaxel), and DNA modifying/alkylating agents (cisplatin, cyclophosphamide).[46,47] The synergistic properties of the oxaliplatin/5-FU combination were maintained in 5-FU–resistant cell lines and in A2780-DDP (cisplatin-resistant) ovarian cells. Additionally, synergy with gemcitabine was recently observed in MMR-deficient HCT116 and c-*myc*–amplified Colo 320 DM colon cancer cell lines.[48] Interestingly, the human lung cancer MV-522 xenograft, in which paclitaxel is active as a single agent, was highly sensitive in combination studies, as exemplified by several cases of significant tumor shrinkage with a combination of paclitaxel, oxaliplatin, and tirapazamine. Although oxaliplatin demonstrates additive/synergistic activity in combination with many standard anticancer agents in preclinical models, some oxaliplatin combinations do not demonstrate increased activity and are sometimes associated with increased toxicity. Consequently, the clinical utility of these oxaliplatin combinations requires the demonstration of clinical efficacy with acceptable safety.

CONCLUSION

Years of experience with cisplatin, one of the most useful antitumor agents available, have shown that many tumors are intrinsically resistant and that many more will acquire resistance during the course of therapy. That many tumors resistant to cisplatin are also resistant to carboplatin results from their sharing a common intermediate capable of reacting with DNA after intracellular transformation. Therefore, out of necessity, novel platinum agents that are converted to different reactive species have been introduced. Oxaliplatin is one such agent, distinct from cisplatin and carboplatin in that the reactive intermediate includes a bulky and rigid 1,2-DACH nonleaving carrier group that restricts the freedom of motion about the platinum atom and produces bulkier DNA conjugates.

Early preclinical studies demonstrated that

Table 5. Oxaliplatin-Based Combinations That Have Demonstrated Additive and/or Synergistic Activity Against Tumor Cell Lines In Vitro and In Vivo

Combinations	In Vitro	In Vivo
Oxaliplatin + 5-fluorouracil (5-FU)	HT29, HT29-5-FU, CaCo2 (colon)[52]	HT29 (colon) xenograft[52]
	2008, A2780, A2780-DDP (ovary)[52]	GR1 (mouse mammary) tumor[52]
	MDA-MB-231 (breast)[52]	L1210 leukemia[45]
Oxaliplatin + gemcitabine	HCT116, Colo 320 DM (colon)	Not evaluated
	CEM (leukemia)[48]	
Oxaliplatin + SN38 or CPT-11	HT29 (colon)[46]	GR1 (mouse mammary) tumor[46]
Oxaliplatin + AG337	HT29 (colon)[52]	GR1 (mouse mammary) tumor[52]
	2008 (breast)[52]	
Oxaliplatin + paclitaxel + tirapazamine	Not evaluated	MV-522 xenograft
Oxaliplatin + cisplatin	KB (cervix squamous cell)[5]	L1210 (leukemia)[53]
	A2780 (ovary)[5]	
Oxaliplatin + CBDCA	Not evaluated	L1210 (leukemia)[53]

many tumors with either intrinsic or acquired resistance to cisplatin responded to oxaliplatin. However, the degrees of cross-resistance are variable. The reason for this variability seems to result from multiple modes of resistance and their simultaneous presence in any given cancer cell. Resistance mechanisms that have been identified include glutathione-based scavenging, increased efflux, reduced accumulation, and genomic-based effects such as MMR deficiency and enhanced replicative bypass. The absence of cross-resistance between oxaliplatin and cisplatin has been specifically correlated with MMR deficiency; it is also associated with effectiveness of the replicative bypass process responsible for cisplatin resistance.

Observations relating to certain specific molecular events at the origin of human carcinogenesis or to the time of progression of the disease indicate that oxaliplatin may be a DNA interacting agent of choice, either alone or in combination. Whereas cisplatin is as effective as oxaliplatin in sensitive cancer cells, the choice of cisplatin may be ultimately determined by issues of clinical tolerance and patient profile compatibility. The observed synergism of oxaliplatin with cisplatin suggests that this association should be further explored. As with other potential combination therapies, determination of the most appropriate sequence of oxaliplatin and cisplatin administration should be actively pursued to provide a rational basis for their use in clinical chemotherapy. Additionally, because of the reduced opportunities for resistance to develop with oxaliplatin, first-line therapy with this agent may curtail the development of significant therapy-dependent resistance and leave more second-line therapy options open at the time of failure. The full clinical potential of oxaliplatin resides in the successful development of oxaliplatin-based combination therapies.

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Pharmacokinetics and Safety Profile of Oxaliplatin

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In early clinical trials, oxaliplatin has demonstrated significant activity against colorectal cancer, both as a single agent and in combination with 5-fluorouracil (5-FU) and folinic acid (FA). Oxaliplatin differs from cisplatin in its lack of nephrotoxicity and from carboplatin in its hematologic toxicity being mild. The most constant acute side effect of oxaliplatin observed in clinical trials was a transient peripheral neuropathy manifesting as paresthesia and dysesthesia in the extremities, triggered or enhanced by exposure to cold. The neurosensory phenomena, dependent on the cumulative dose of oxaliplatin, affect all patients who receive doses ≥540 mg/m^2 over four cycles or more of therapy. This neurologic toxicity is also highly reversible, with 82% of patients having their neuropathy regress within 4 to 6 months and 41% experiencing complete recovery within 6 to 8 months. With these considerations in mind, the currently recommended dosing schedules for oxaliplatin are 130 mg/m^2/d as a 2- to 6-hour infusion or 175 mg/m^2/d as a chronomodulated infusion over 5 days, both of which are administered every 3 weeks. Oxaliplatin rapidly disappears from the plasma and is rapidly transformed into putative active species. 5-Fluorouracil and folinic acid, often used in combination with oxaliplatin, do not affect its pharmacokinetics. The favorable pharmacokinetics and safety profile of oxaliplatin contribute to its tolerability, particularly in pretreated cancer patients with reduced renal function. The reversible nature of its dose-limiting neurotoxicity and its synergistic action with 5-FU/FA make oxaliplatin an interesting agent for the treatment of colorectal cancer and for other potential indications.

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OXALIPLATIN, a third-generation antineoplastic platinum coordination complex of the 1,2-diaminocyclohexane family, has shown significant activity in preclinical studies against murine leukemia,[1-4] lymphoma,[3] melanoma,[4] lung[3,4] and colon carcinoma,[4] and fibrosarcoma,[4] and in human cancer cell lines from ovarian cancer,[5] non–small cell lung cancer,[6] neuroblastoma,[7] nonseminomatous germ cells,[8] erythroleukemia,[9] and breast[9] and colon cancer.[9] Oxaliplatin was introduced into clinical trials by Mathé et al in 1986.[10] Additional phase I studies were subsequently conducted to establish the pharmacokinetic properties, tolerability, and maximal tolerated dose (MTD) of oxaliplatin. Cumulative neurotoxicity as well as other oxaliplatin-associated effects related to dose per cycle and multiple-dose treatments have been assessed in large patient cohorts, both prospectively and retrospectively. The formal assessment of the pharmacodynamics of oxaliplatin in phase I and II trials has confirmed its favorable toxicity and safety profile.

PHASE I STUDIES AND SAFETY PROFILE

Short-Term Administration

In the original phase I study, 23 patients received oxaliplatin as a short infusion (≤30 minutes) every 3 to 4 weeks. The study design specifically allowed for accelerated intrapatient dose escalation in the overall dose per cycle range from 0.45 mg/m^2 to 67 mg/m^2. Dose-limiting toxicity was not observed and an MTD could not be determined.[10] Despite the low dose of oxaliplatin, one partial response and one complete response were recorded. Additionally, the lack of nephrotoxicity and moderate emesis suggested that the toxicity profile of oxaliplatin differs from that of cisplatin. The investigators therefore recommended a high starting dose for further investigation.

A larger phase I study of 44 patients with advanced cancer was reported in 1990 by Extra et al.[11] In this trial, patients received 116 courses of oxaliplatin escalated intrapatient through seven levels, from a starting dose of 45 mg/m^2, as recommended by Mathé et al,[10] to 200 mg/m^2. The duration of administration varied from 30 minutes to 2 hours. Most patients had received prior chemotherapy, some of which included cisplatin. Since nephrotoxicity had not been observed in the earlier dose-escalation study, oxaliplatin was administered without prehydration or posthydration. World Health Organization (WHO) grade 2 transient creatinine elevation seen in five of 116 treatment cycles was not causally related to oxaliplatin use. All patients experienced nausea and vomiting, but the severity of emesis did not appear to be

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Table 1. Grade 3 and 4 Toxicities* Observed in Phase I Trials as a Function of Oxaliplatin Dose Administered as a 2-Hour Infusion

Toxicity	Dose, mg/m² (%)			
	≤90 (n = 40)	130-135 (n = 18)	150-180 (n = 27)	200 (n = 12)
Neutropenia	1 (2.5)	1 (5)	5 (18)	4 (33)
Thrombocytopenia	0	0	1 (4)	0
Anemia	0	0	0	0
Nausea/vomiting	7 (17)	13 (72)	13 (48)	8 (67)
Acute neurotoxicity	1 (2.5)	3 (17)	9 (33)	3 (25)
Diarrhea	0	0	3 (11)	4 (33)

* Based on WHO scale.

dose related, except at the highest dose (Table 1). Extending the length of infusion did not reduce the symptoms, but systematic pretreatment with antiemetics reduced grade 3 or 4 nausea and vomiting to 11%.[10,11] Gastrointestinal toxicity was also recorded as mostly grade 1 or 2 diarrhea in 24% of therapy courses (Table 1).[11]

Hematologic toxicity was moderate. Thrombocytopenia was dose related and did not occur at doses less than 90 mg/m² of oxaliplatin, but 13% of patients receiving 135 to 150 mg/m² and 28.5% of those receiving 175 to 200 mg/m² exhibited a decreased platelet count that never exceeded grade 2.[11] Similarly, only grade 1 or 2 neutropenia was observed, and hemoglobin levels remained mostly unchanged (Table 1).[11] The incidence of myelosuppression resulting from oxaliplatin therapy was significantly lower than would be expected from a regimen that included therapeutic doses of carboplatin.[12]

The most constant acute side effect of oxaliplatin administration was a transient peripheral neuropathy manifesting as paresthesia and dysesthesia in the extremities and perioral area, triggered or enhanced by exposure to cold. These symptoms, often developing during oxaliplatin infusion, lasted between a few minutes and a few days. This toxicity usually appeared at doses ≥ 90 mg/m² and affected up to 75% of patients treated with 200 mg/m² oxaliplatin (Table 1). The duration and intensity of the symptoms increased with the number of courses administered. Thus, the neurologic toxicity observed in this trial was cumulative. Grade 3 neurologic toxicity occurred in 6% of cycles and 14% of patients, and an MTD of 200 mg/m² was defined. These data were confirmed by Chevallier and Armand with high-dose (>175 mg/m²) oxaliplatin in two subsequent small confirmatory phase I experiences involving 10 patients (personal communication, November 1997). At such high doses, oxaliplatin also induced severe nausea and vomiting in up to 20% of patients, but minimal hematologic toxicity. Grade 3 neurotoxicity has been observed at cumulative doses greater than 540 mg/m². A transient laryngospasm-like syndrome and mild ataxia have occurred in patients receiving the highest doses and in those pretreated with cisplatin.[11] The neurosensory phenomena affect all patients treated with over four cycles of therapy and, although not formally defined, 200 mg/m² is usually considered the MTD; the recommended dose (RD) is 130 mg/m² per cycle repeated every 3 weeks as a 2- to 6-hour infusion.

The morphologic changes associated with the sensory neuropathy of oxaliplatin therapy have been characterized with both light and electron microscopy. Biopsy specimens taken from four patients receiving single doses of 175 to 200 mg/m² oxaliplatin revealed minimal axonal lesions and limited wallerian degeneration under light microscopy. Electron microscopy also revealed an increased density of collagen pockets in all four patients. The investigators suggested that dysesthetic symptoms may be associated with the development of collagen pockets, resulting from a slight decrease in the density of small myelinated fibers.

Neurotoxicity Issues

Phase I and II studies indicate that peripheral neuropathy, the most severe toxicity resulting from oxaliplatin therapy, can be maintained at ≤grade

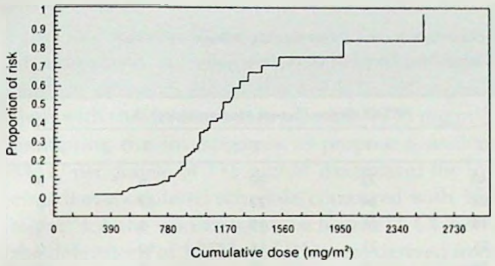

Fig 1. Risk of developing severe neurotoxicity (grade ≥ 3 specific scale) depending on the cumulative dose (mg/m²) of oxaliplatin.

2 at the RD of 130 mg/m^2. The neurotoxic profile of oxaliplatin is particular in its reversibility, as well as in its rapid onset, location, and intensity of sensory disturbance with the absence of a motor component.

In a recent overall evaluation of safety in 682 patients who had received oxaliplatin either as a single dose or in combination with 5-fluorouracil (5-FU), grade 3 neurotoxicity (specific scale) presenting as fine movement disturbance (such as buttoning) or moderate sensitive ataxia was observed in 12% of patients at a median cumulative dose of 900 mg/m^2 oxaliplatin (Brienza et al[13] and Brienza, unpublished data). The risk of developing severe disturbance of neurologic function with respect to the cumulative dose administered was assessed according to a Kaplan-Meier model (Fig 1). This evaluation demonstrated that the total cumulative dose of oxaliplatin is the most significant prognostic factor used for assessing neurotoxic risk. For instance, total cumulative doses of 780 mg/m^2, 1,170 mg/m^2, and 1,560 mg/m^2 have been correlated with an incidence of 10%, 50%, and 75% neurotoxic risks, respectively. Additionally, a significant correlation ($P = 10^{-5}$) between regression of neurologic symptoms and total cumulative dose administered has been demonstrated (Brienza, unpublished data). Symptoms resulting from ≥ grade 2 neuropathy have also been shown to regress in 82% of patients within 4 to 6 months and have disappeared entirely in 41% of patients within 6 to 8 months.[13]

Two consecutive phase II studies have confirmed that the severity of neurotoxicity depends on the cumulative dose administered (Table 2) and that it is mostly or completely reversible.[14] During long-term follow-up of seven patients with grade 3 neuropathy, five had complete disappearance of symptoms and two had major attenuation of symptoms within 5 months of discontinuing oxaliplatin. Of three patients with grade 4 neuropathy, one had complete disappearance of symptoms within 2 months and two had partial regression at 3 months and 5 months, respectively.[14]

The assessment of oxaliplatin neurotoxicity showed that the neurologic toxicity scales currently available (National Cancer Institute-Cancer Treatment Center, WHO) are generally insufficient for grading the characteristics of dysesthesia associated with oxaliplatin treatment and for assessing the gravity of the symptoms. None of the scales allow for an evaluation of neurotoxic symptoms that includes both intensity and duration. A specific neurotoxicity scale for the assessment of oxaliplatin-induced paresthesia/dysesthesia was therefore developed by Lévi's group.[15] The proposed scale provides a grading system that takes into account both intensity and duration of symptoms. A comparative evaluation of the proposed scale and the WHO scale was provided by Machover et al.[14] In the oxaliplatin specific scale, grade 3 refers to a gradual increase in both the severity and duration of the neurosensory symptoms that become permanent during successive 3-week cycles of oxaliplatin. Moderate functional impairment, including buttoning difficulty and rapid writing, are considered grade 4, as are mild signs of ataxia from proprioception deficit. Grade 4 of the oxaliplatin specific scale is equivalent to grade 3 of the WHO scale.

In all studies reported to date, the neurotoxicity resulting from oxaliplatin treatment was shown to be specific, cumulative, and, unlike cisplatin-induced neuropathy, reversible. In a recent study by Misset et al[16] of 176 stage III or IV ovarian cancer patients treated with cyclophosphamide (1,000 mg/m^2) and either cisplatin (100 mg/m^2) or oxaliplatin (130 mg/m^2), the incidence of neuropathy was higher in the oxaliplatin arm but was rarely severe, decreasing or disappearing after treatment, whereas cisplatin-induced neuropathy tended to increase posttreatment without showing signs of reversibility (Table 3).

Because ototoxicity leading to permanent hearing impairment is also a concern with cisplatin therapy, patients with head and neck cancer treated either with oxaliplatin (130 mg/m^2) or conventional cisplatin (100 mg/m^2) plus 5-FU (1,000

Table 2. Proportion of Patients With Advanced Colorectal Carcinoma Experiencing Adverse Events in Phase II Trials as a Function of the Cumulative Doses of Oxaliplatin

Adverse Events	Cumulative Dose (mg/m^2)	WHO Grade (Except Neurotoxicity) (%)				
		0	1	2	3	4
Nausea/vomiting	390	40	22	30	6	2
	650	26	34	23	17	0
Diarrhea	390	70	11	19	0	0
	650	55	21	14	10	0
Granulocytopenia	390	94	6	0	0	0
	650	89	5	4	2	0
Anemia	390	74	19	5	2	0
	650	65	27	6	2	0
Thrombocytopenia	390	88	8	4	0	0
	650	77	9	14	0	0
Neurotoxicity (specific scale)	390	4	37	41	14	4
	650	2	28	39	23	8
Nephrotoxicity	390	100	0	0	0	0
	650	95	5	0	0	0

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$mg/m^2/d$) were evaluated audiometrically.[17] Cisplatin was found to be significantly more ototoxic than oxaliplatin. In the cisplatin-treated group, nine of 16 patients (56%) developed significant hearing loss, whereas only two of 15 (13%) in the oxaliplatin-treated group developed mild hearing loss confined to the high-frequency range,[17] which is characteristic of presbycusis rather than of ototoxicity.

Table 3. Neurotoxicity Comparison Between Cisplatin and Oxaliplatin

	Cisplatin, 100 mg/m^2 (%)	Oxaliplatin, 130 mg/m^2 (%)
No. of patients	91	85
Cumulative dose administered	481.9 ± 162.5	643.4 ± 180
Neurologic WHO toxicity		
Grade 1/2	24/91 (27)	55/85 (65)
Grade 3/4	2/91 (2)	0/85 (0)
Neurotoxicity at completion	17/91 (19)	41/85 (48)
Complete resolution within 6 months	1/17 (6)	14/41 (34)
Worsening after completion	4/17 (24)	1/41 (2.4)
Occurrence after completion	12/74 (16)	4/44 (9)

Continuous Infusion

The efficacy of antineoplastic therapy is intimately related to the dose of anticancer agent that can be administered without causing undue toxicity to the patient.[18] Extended infusions of chemotherapeutic drugs have long been known to modify the toxicity profile. In phase I trials, continuous infusion of cisplatin was demonstrated to be safe, and in some instances toxicity was reduced.[19] Additionally, because rodent studies have shown that cisplatin toxicity can be significantly decreased by timing drug delivery according to the circadian rhythm,[20] chronomodulated delivery has been applied to oxaliplatin therapy and extensively studied.

In an open, randomized phase I study comparing extended, constant-dose infusion and chronomodulated infusion, oxaliplatin dosage was escalated for each course, from 125 mg/m^2 to 200 mg/m^2 in 25 mg/m^2 increments.[15] The incidence of neutropenia was lower (≤grade 2) with the circadian-modulated schedule than with the constant-rate infusion schedule (2% *v* 19% of administered courses; $P = .05$). The incidence of peripheral paresthesia (≥grade 2) was also reduced (2% *v* 28% of the administered courses; $P = .001$). Four of the 11 patients on the circadian-modulated schedule received the targeted final dose; in contrast, none of the 12 patients enrolled completed the con-

stant-rate schedule. Consequently, the mean dose of oxaliplatin delivered was significantly higher with the circadian modulated schedule (180 mg/m^2) than with the constant-rate schedule (135 mg/m^2), prompting the investigators to propose a median MTD per course of 175 mg/m^2 oxaliplatin for the circadian-modulated schedule compared with 150 mg/m^2 for the constant-rate schedule.[15] Of note, the definitions of MTD and RD were derived from a low median number of cycles per patient. The insight gained from the cumulative nature of the neurotoxic phenomena from several hundred patients treated with combination oxaliplatin/5-FU therapy led to a downward reappraisal of these values. Accordingly, circadian-modulated delivery schedules have been developed to deliver higher levels of drug and reduce dose-limiting toxicity in an attempt to enhance activity.[21-28]

Reduced toxicity was demonstrated in a recently published phase III trial[22] comparing a triweekly schedule of either constant infusion or chronomodulated administration of oxaliplatin (125 mg/m^2) in combination with 5-FU/folinic acid (FA). In this study, functional impairment occurred twice as often in patients receiving the constant-rate schedule (31% v 15%). Accordingly, the satisfactory safety profile has allowed the administration of such chronomodulated schedules as a biweekly regimen, permitting the delivery of a more intense dose at a rate of 100 mg/m^2 per cycle oxaliplatin for up to seven cycles (cumulative dose, 700 mg/m^2), followed by continued administration for up to 12 weeks at a rate of 30 to 40 mg/m^2/wk.[24]

Safety Issues and Recommended Dose

Overall, the safety data on oxaliplatin confirm a toxicity profile that is clearly differentiated from those of other platinum agents. Oxaliplatin demonstrates a lack of nephrotoxicity, even in the absence of patient hydration, minimal ototoxicity, and minimal hematologic toxicity. The gastrointestinal side effects inherent to platinum chemotherapy have been effectively controlled with standard antiemetics and antidiarrheal agents. Neurotoxicity usually regresses on cessation of oxaliplatin treatment and in many cases is completely reversible. Regression of neurotoxicity is particular to oxaliplatin; it has not been observed with either cisplatin or ormaplatin, another *trans-l*-diaminocyclohexane platinum derivative.[29,30]

Although a correlation between neuropathy and single-dose administration of oxaliplatin is evident, a clearly defined MTD has not been established, but it is estimated to be approximately 200 mg/m^2. In general, the total cumulative dose is considered to be more predictive of toxic risk than is the MTD. Consequently, current RD schedules, based on estimated median cumulative levels, are as follows: 130 mg/m^2/d as a 2-hour intravenous infusion in normal saline every 3 weeks or 125-150 mg/m^2/d as a chronomodulated intravenous infusion over 5 days per week every 3 weeks.

BIOTRANSFORMATION OF OXALIPLATIN

The hydrolytic breakdown of 1,2-diaminocyclohexane platinum malonate, a compound expected to have chemical properties similar to those of oxaliplatin, has been studied in detail.[31] From these studies it can be inferred that once oxaliplatin enters the bloodstream, the oxalate moiety is rapidly displaced by bicarbonate ions and the resulting unstable species is converted first to a monoaquate and ultimately to a diaquate. The aquated species predominate intracellularly and ultimately react with cellular DNA to form adducts that hamper DNA replication.[32]

Human studies have shown that approximately 85% of plasma oxaliplatin rapidly becomes protein bound[33]; a significant proportion (37%) of the infused drug becomes sequestered in erythrocytes within 2 to 5 hours of exposure.[34] Simultaneously, within 2 hours after infusion, oxaliplatin disappears from the plasma ultrafiltrate and is undetectable in the urine. Major biotransformation products of oxaliplatin have been identified in the plasma ultrafiltrate and include (*trans*-1,2-diaminocyclohexane) dichloroplatinum, (*trans*-1,2-diaminocyclohexane) monochloromonoaquoplatinum, methionine (*trans*-1,2-diaminocyclohexane) platinum, and glutathione (*trans*-1,2-diaminocyclohexane) platinum (ref 34 and D. Greenslade, personal communication, March 1998). These compounds, together with (*trans*-1,2-diaminocyclohexane) diaquoplatinum and free diaminocyclohexane, also have been identified in the urine of patients.

Recent studies of patients with colorectal cancer confirmed that oxaliplatin platinum is partitioned rapidly into three compartments of unequal importance: protein-bound plasma platinum, free plasma platinum, and erythrocyte-sequestered platinum. The proportion of protein-bound platinum in-

creased over time, from 70% 2 hours after infusion to 95% after 5 days. Approximately half of the platinum dose was recovered in the urine within 3 days of administration, whereas fecal excretion was minimal. Mass balance is significantly shorter than that of cisplatin (20 days) and somewhat longer than that of carboplatin (6 hours). By day 11, 57% of the infused platinum had been recovered in the urine and 5% in the feces.[35]

PHARMACOKINETICS

Clinical Studies

Until recently, clinical pharmacology studies of oxaliplatin used the classic method of flame atomic absorption to determine serum platinum levels. In these early pharmacokinetic studies, it was shown that the route of oxaliplatin administration, whether intravenously or intraperitoneally, had little effect on distribution and clearance, but significantly influenced the time to maximum plasma levels and the maximum concentration reached.[36] The pharmacokinetic behavior of oxaliplatin has also been evaluated in patients with normal or impaired kidney function (creatinine clearance value, < 60 mL/min).[37,38] Administered as a short 2-hour infusion, both oxaliplatin and cisplatin exhibited a very high volume of distribution and dual compartmentalization for total and ultrafiltrable platinum.[39] There were no differences in C_{max} of platinum in either plasma or ultrafiltrate; however, the AUC of ultrafiltrable platinum in renally impaired patients was significantly increased (Table 4).[38] This suggested that at the MTD, oxaliplatin could be administered equally safely both to nephronormal patients and to those with moderate renal impairment without requiring dose adjustment or hydration.

Table 4. Comparison of Oxaliplatin Pharmacokinetic Parameters in Patients With Normal and Impaired Renal Function

	Nephronormal (n = 14)	Impaired (n = 10)	*P* Value
Peak plasma levels (μg/mL)			
T Pt	5.1 ± 0.2	4.9 ± 0.3	NS
UF Pt	2.1 ± 0.2	2.3 ± 0.4	NS
AUC (μg/mL/hr)			
T Pt	102.8 ± 6.6	119.7 ± 18.9	NS
UF Pt	9.8 ± 0.9	15.2 ± 1.4	.004
Clearance (L/hr)			
T Pt	2.4 ± 0.2	1.9 ± 0.2	NS
UF Pt	26.5 ± 2.1	15.1 ± 1.7	0009
$T_{1/2\alpha}$ (hr)			
T Pt	0.43 ± 0.1	0.69 ± 0.3	NS
UF Pt	0.35 ± 0.1	0.49 ± 0.2	NS
$T_{1/2}\beta$ (hr)			
T Pt	38.7 ± 2.4	54.9 ± 8.9	NS
UF Pt	24.2 ± 6.9	27.7 ± 4.1	NS
V_d (L)			
T Pt	70.5 ± 4.4	58.1 ± 2.8	NS
UF Pt	330.1 ± 40.9	240.8 ± 31.1	.02
% Urinary excretion (at 48 hr)	>50%	<30%	

Abbreviations: T Pt, total platinum; UF Pt, ultrafiltrable platinum; AUC, area under the curve; $T_{1/2}$, half-life; V_d, volume of distribution.

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Patients who receive chronomodulated therapy are exposed to changing levels of oxaliplatin over time. A recent study assessed the relationship between peak time drug delivery, platinum levels, and toxicity. Free and total plasma platinum levels were determined in 36 patients treated with chronomodulated oxaliplatin (25 mg/m^2/d), 5-FU (800 mg/m^2/d), and FA (150 mg/m^2/d) over a 4-day period. Results showed plasma platinum and free platinum levels, as well as overall toxicity, to be dependent on the time of oxaliplatin infusion (Table 5).[40]

Currently, the more powerful technique of inductively coupled plasma-mass spectrometry has been applied to determine the pharmacokinetic behavior of oxaliplatin.[33] The sensitivity of this procedure allows for the determination of platinum levels in red blood cells and plasma (differentiated as ultrafiltrable, plasma protein-bound, and soluble platinum). The red blood cells, plasma, and ultrafiltrable platinum are measured by mass spectrometry, with a sensitivity that allows for the determination of platinum levels 3 weeks after administration.

Inductively Coupled Plasma-Mass Spectrometry Studies

The pharmacokinetics of oxaliplatin platinum have been evaluated in the plasma, plasma ultrafiltrate, and red blood cells of 26 patients with advanced cancer treated with 130 mg/m^2 via 2-hour intravenous infusions every 3 weeks. Platinum levels were determined by inductively coupled plasma-

Table 5. Pharmacokinetic Characteristics of Oxaliplatin Infused at Various Times of the Circadian Rhythm and Subsequent Toxicities

	Schedule			
	−9 (7:00 AM)	0 (4:00 PM)	+9 (1:00 AM)	*P* Value (ANOVA)
Total Pt. C_{max} (ng/mL)	1171 ± 249	1004 ± 217	701 ± 177	.001
Free Pt. C_{max} (ng/mL)	236 ± 24	185 ± 24	123 ± 20	.003
Toxicity (oxaliplatin-specific grade 3-4)				
Diarrhea	4/15 (27%)	1/6 (17%)	4/15 (27%)	
Peripheral neuropathy	0/15 (0%)	0/6 (0%)	3/15 (20%)	

NOTE. Three delivery schedules were compared: a standard infusion time at 4:00 PM (0), and infusion times 9 hours before (−9) or 9 hours after (+9).

Abbreviations: Pt, platinum; C_{max}, maximum concentration of drug.

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mass spectrometry with a limit of detection of 1 ng/mL in ultrafiltrate and 100 ng/mL in plasma and red blood cells. Oxaliplatin was distributed extensively in plasma and in ultrafiltrate. Plasma protein binding was high and did not change throughout five cycles of therapy. The elimination of oxaliplatin was slow, with 33% eliminated within 48 hours, but residual levels were still detectable 63 days posttreatment (Table 6).

The long-term administration of cisplatin leads to neuropathy and ototoxicity, both of which depend on the cumulative dose of platinum achieved in neuronal tissue. Cisplatin also accumulates in the plasma[41]; this is attributed to rapid uptake into red blood cells, followed by a long (29.8-day) terminal half-life.[39] Whether this effect is related to cisplatin toxicity or reflects normal red blood cell turnover remains an open question. The cumulative pharmacokinetics of oxaliplatin have recently been evaluated to determine platinum distribution, infer potential toxicities, and assess the risks of permanent tissue damage.[33] Patients with metastatic colorectal cancer received conventional short-term (2-hour) oxaliplatin infusions every 3 weeks. 5-Fluorouracil and FA were administered concomitantly on a weekly basis. The maximum oxaliplatin concentration was reached within 2 hours of administration, and platinum levels decayed rapidly within 8 days (Table 7). Total plasma platinum did not accumulate to any meaningful extent after seven courses of therapy, as does cisplatin-derived platinum.[41] However, platinum of oxaliplatin origin accumulated in red blood cells, with a mean terminal half-life of 48 ± 10 days consistent with that of erythrocytes.[34] Red blood cell platinum from oxaliplatin administration does not appear to be exchangeable into plasma. Consequently, the intraerythrocyte platinum does not, in the short term, contribute to the maintenance of platinum plasma levels.[34] These observations may explain in part the rapid clearance of oxaliplatin compared with cisplatin, the lack of oxaliplatin nephrotoxicity, and the reversible, rather than permanent, neurotoxicity observed in phase I trials.

Table 6. Pharmacokinetics of Oxaliplatin Administered as a 2-Hour Infusion of 130 mg/m² Every 3 Weeks: Determination by Inductively Coupled Plasma-Mass Spectrometry

	Plasma	Ultrafiltrate	Red Blood Cells
C_{end}	3.61 ± 0.43	1.21 ± 0.10	3.00 ± 0.33
C_{max}	3.61 ± 0.43	1.21 ± 0.10	3.25 ± 0.49
AUC_{0-48} (μg/mL · hr)	79.9 ± 14.7	8.2 ± 2.4	151.0 ± 41
$AUC_{0-\infty}$ (μg/mL · hr)	207.0 ± 60.9	11.9 ± 4.6	1,326.0 ± 570
$T_{1/2}\alpha$ (hr)	7.3 ± 4.9	0.28 ± 0.06	589.0 ± 89.9
$T_{1/2}\beta$ (hr)	239.0 ± 54.4	16.3 ± 2.9	NA
$T_{1/2}\gamma$ (hr)	NA	273.0 ± 19	NA
V_{ss} (L)	93.4 ± 16.8	582.0 ± 261	NA
Clearance (L/hr)	0.56 ± 0.10	10.10 ± 3.07	0.09 ± 0.03

Abbreviations: C_{end}, concentration of drug at end of infusion; C_{max}, maximum concentration of drug; AUC, area under the curve; $T_{1/2}$, half-life; V_{ss}, apparent volume of distribution; NA, not applicable.

From M. Graham (personal communication, March 1998).

Table 7. Total Platinum Concentration at Peak (2 Hours After Infusion, C_{max}) and Immediately Preceding the Next Oxaliplatin Infusion (Day 22; C_{min}) in Patients With Colorectal Cancer Receiving Six or More Cycles of Therapy

	Cycle						
Platinum (mg/L)	1	2	3	4	5	6	7
Total							
C_{max}	3,201 ± 60	3,349 ± 796	3,095 ± 542	2,619 ± 805	2,914 ± 571	3,526 ± 1,307	4,475 ± 933
C_{min}	161 ± 45	187 ± 31	189 ± 31	200 ± 13	225 ± 22	244 ± 43	250 ± 80

Abbreviations: C_{max}, maximum concentration of drug; C_{min}, minimum concentration of drug.

Pharmacokinetic Interactions in Combination Therapy

Current pharmacokinetic data indicate that the 5-FU/FA combination does not influence the pharmacokinetics of oxaliplatin.[33] Preclinical studies have shown that combining oxaliplatin with either cisplatin or carboplatin results in synergistic and supra-additive antineoplastic activity.[42] However, it is worth noting that the pharmacokinetic profile of oxaliplatin is more akin to that of cisplatin than to carboplatin. An ongoing phase I study is evaluating the pharmacokinetics and safety profile of the oxaliplatin/carboplatin combination in patients with advanced malignancies. Preliminary data, obtained at a carboplatin ultrafiltrable area under the curve of 4.1 resulting from carboplatin administration 1 hour before oxaliplatin administration, show a high incidence of grade 3/4 hematologic toxicity. However, peripheral neuropathy did not exceed grade 1.[43]

A recent study of the irinotecan/oxaliplatin combination for colorectal cancer has shown that the area under the curves of irinotecan and metabolites administered at a dose of 150 to 200 mg/m^2 in the presence of 85 to 110 mg/m^2 oxaliplatin are identical to the irinotecan area under the curve obtained when this drug is used alone at a dose of 350 mg/m^2.[44]

CONCLUSION

Pharmacokinetic and preliminary studies in humans have shown that oxaliplatin can be administered safely at a dose of 130 mg/m^2 over a 2-hour infusion. Under these conditions, nephrotoxicity, a major dose-limiting toxicity of cisplatin, is nonexistent, and hematologic toxicity, a major dose-limiting toxicity of carboplatin, is moderate and usually confined to ≤grade 2. Gastrointestinal toxicity, apparent as nausea and vomiting, can be controlled with systematic antiemetic treatment. Diarrhea occurs at ≤grade 2 in approximately one quarter of patients. Sensory neuropathy is a dose-limiting toxicity of oxaliplatin; however, at the RD, less than 8% of patients experience severe neurotoxicity after six cycles of therapy at a cumulative dose of 780 mg/m^2.

The pharmacokinetic profile of oxaliplatin, with high clearance rates, high volume of distribution, and faster elimination than cisplatin, results in no nephrotoxicity. This allows for the use of oxaliplatin in patients with renal impairment without modification of schedule or pretreatment or posttreatment hydration. This is a significant advantage, particularly in relapsed patients whose therapy options are often limited by reduced kidney function attributable to previous therapies, including nephrotoxic antibiotics used to control infections during neutropenic episodes. Patients receiving chronomodulated oxaliplatin infusions were able to tolerate a higher mean dose per cycle of 180 mg/m^2 with comparatively lower toxicity than with a constant-rate schedule over short treatment periods.

Oxaliplatin is currently being tested in the colorectal cancer therapy setting. It has provided significant response rates alone and enhanced the response to the 5-FU/FA regimen. Other cancer types susceptible to oxaliplatin therapy are currently being identified or challenged in phase I studies. Additional phase I studies are needed to explore alternative schedules of administration and potential combination therapies.

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Clinical Efficacy of Oxaliplatin Monotherapy: Phase II Trials in Advanced Colorectal Cancer

Yves Becouarn and Philippe Rougier

For the past 40 years, the mainstay of chemotherapy against colorectal cancer has been 5-fluorouracil (5-FU), often administered in recent years with folinic acid modulation. Traditional platinum derivatives have generally been ineffective in colorectal cancer therapy; however, the third-generation 1,2-diaminocyclohexane-platinum derivative oxaliplatin has shown good antitumor activity and a lack of cross-reactivity with cisplatin. Oddly, oxaliplatin was first developed as a combination therapy with 5-FU plus folinic acid administered as a chronomodulated infusion over 5 days. In subsequent phase II clinical trials, the activity of single-agent oxaliplatin was assessed in 63 previously untreated patients and 139 patients with metastatic disease refractory to 5-FU. In first-line therapy, the median overall survival was approximately 13 to 14 months, whereas in previously treated patients no longer responding to 5-FU, it was 8 to 10 months. The 18% objective response rate obtained with first-line therapy confirms that the activity of single-agent oxaliplatin is comparable to other anticancer therapies considered active against colorectal cancer. The 10% response rate obtained in second-line therapy in patients refractory to 5-FU provides a means for palliative care and suggests the possibility for a potentially active combination regimen with 5-FU.

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THE INCIDENCE of colorectal cancer varies by geographic location worldwide, with the highest rates reported from Australia, New Zealand, North America, and certain countries in northern and western Europe.[1-3] More than 300,000 new cases are diagnosed in the United States and Europe each year.[4] Despite a decline in the incidence and mortality rates of colorectal cancer in recent years, this malignancy ranked fourth in estimated new cancer cases in 1997 in the United States, exceeded only by prostate, breast, and lung cancer, and ranked second in estimated cancer deaths, accounting for 10% of all cancer deaths.[5,6]

TREATMENT OPTIONS FOR ADVANCED COLORECTAL CANCER

The main potentially curative treatment option for patients with colorectal cancer is surgical resection, but more than 50% of patients eventually die of metastatic disease progression.[4,7] Since its introduction into clinical practice 40 years ago, the mainstay of chemotherapy for advanced colorectal cancer has been 5-fluorouracil (5-FU).[1,8] The outcome with 5-FU administered as a single agent by intravenous bolus to patients with metastatic colonic cancer, however, has been far from ideal, with response rates usually ≤15% and median survival times of 6 to 9 months.[1,8,9]

Attempts to increase the efficacy of 5-FU in chemotherapy-naive patients have included (1) modification of the route and schedule of administration of 5-FU; (2) combination of 5-FU with other cytotoxic agents, such as semustine (methyl-CCNU [lomustine]), mitomycin C, or cisplatin; (3) biochemical modulation of the cytotoxicity of 5-FU by combination with folinic acid (FA), methotrexate, alpha interferon, PALA, or other modulators; and (4) local/regional administration, such as direct hepatic arterial infusion for patients with liver metastases.[1,2,4,7-11] Some of these first-line systemic approaches have improved response rates up to 30%. In particular, the modulation of 5-FU by FA is routinely used, having yielded response rates that were twofold or greater than those of 5-FU alone.[12] Unfortunately, there has been little survival benefit, with the median survival reported in multicenter trials of patients with advanced colorectal cancer seldom exceeding 12 months[13-15]; moreover, many of the combination regimens are associated with increased toxicity and cannot be routinely recommended, and hepatic arterial infusion does not preclude progression of systemic disease and is reserved for specific patient subsets.[1,2,4,7,8,11,14]

The need for alternative or second-line chemotherapy also may be urgent for patients with advanced colorectal cancer after failure of 5-FU–based regimens.[1,4,10,16] Since the discovery of the antitumor activity of cisplatin in the late 1960s, this agent has been found to be effective in the

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Table 1. Antitumor Activity of Single-Agent Cisplatin and Carboplatin in Phase II Trials of Patients With Metastatic Colorectal Cancer

Study	No. of Patients in the Study: Enrolled/ Evaluated	No. of Patients in the Study: Pretreated/ Previously Untreated	Dosage and Schedule ($mg/m^2/d$)	Overall Response Rate (%)	Duration of Response (mo)	Progression-Free Survival (mo)	Median Overall Survival (mo)
Cisplatin							
Kovach et al[24]	32/32	18/14	50 every 5 wk	0	—	—	—
DeSimone et al[22]	54/53	23/31	120 every 3 wk	9	—	—	—
Lokich et al[23]	25/16	25/0	5 CI, 2-35 d	0	—	—	—
Total	111/101	66/45		0-9	—	—	—
Carboplatin							
Nole et al[32]	21/21	21/0	400 every 3 wk	0	—	—	—
Perry et al[33]	30/30	15/15	320-480 every 4 wk	0	—	—	6
Asbury et al[34]	56/56	0/56	400 every 4 wk	5 (1 CR, 2 PR)	—	—	10
Pazdur et al[35]	25/24	1/24	400-450 every 4 wk	4 (1 PR)	6	3	4.5
Schmoll et al[36]	30/30	25/5	360-400	3 (1 PR)	6	—	—
Total	162/161	62/100		0-5	6	3	4.5-10

Abbreviations: CR, complete response; PR, partial response; CI, continuous infusion.

treatment of a wide range of malignancies.[17-20] Although therapy with this platinum drug is associated with dose-limiting neurotoxicity, ototoxicity, and nephrotoxicity, cisplatin is currently the recommended agent of choice for the treatment of several types of solid tumors.[17,20,21] However, neither low-dose nor high-dose cisplatin administered as a single agent appears to be of benefit in patients with advanced colorectal cancer refractory to 5-FU (Table 1).[22-24]

Several new agents are being developed for use in the treatment of advanced colorectal cancer. Most of these agents are thymidylate synthase inhibitors, which were chosen because of their purported biochemical and galenical advantages; raltitrexed, UFT (uracil and tegafur), and capecitabine are the furthest advanced in clinical development.[25-28] An agent with a different mechanism of action is irinotecan (CPT-11), a semisynthetic derivative of camptothecin that acts as a topoisomerase I inhibitor.[29] Overall response rates of 10% to 30% have been achieved with CPT-11 in both chemotherapy-naive patients and refractory pretreated patients with advanced colorectal cancer; tumor growth control for a median duration of 4 months was demonstrated in 58% of patients resistant to 5-FU.[29-31] The major toxicities of CPT-11 are neutropenia and diarrhea, severe (World Health Organization [WHO] grade 3 or 4) in up to 20% and 30% of patients, respectively.[29-31] Further research efforts for newer agents, including cisplatin analogues, have focused on the development of more active and less toxic forms of treatment for this disease.

DEVELOPMENT OF CISPLATIN ANALOGUES

The first commercially available cisplatin derivative was carboplatin, a second-generation platinum analogue with an improved therapeutic index. At effective doses, carboplatin produces significantly less renal toxicity, neurotoxicity, and side effects, such as nausea, emesis, anemia, and alopecia.[17,21,32] Like cisplatin, however, single-agent carboplatin has been shown to be inactive in patients with advanced colorectal cancer that had progressed during therapy with 5-FU and is not recommended for such patients.[32] An overview of several representative phase II trials that demonstrate the weak antitumor efficacy of cisplatin and carboplatin administered as single-agent therapy

to patients with advanced colorectal cancer is presented in Table 1.[32-36]

Among the numerous second- and third-generation cisplatin analogues evaluated in recent years, the 1,2-diaminocyclohexane-platinum compounds have been of most interest because of their stability, good antitumor activity, and lack of cross-resistance with cisplatin.[18,37] One 1,2-diaminocyclohexane compound successfully developed in France in the past decade is oxaliplatin.[38,39] Animal studies have shown that in vivo, this agent is at least as effective if not more effective than cisplatin against solid tumors.[38,39] Studies of the antitumor activity of oxaliplatin have shown this platinum complex to be active in a range of cisplatin-resistant murine leukemia cell lines in vitro and more effective than cisplatin against both cisplatin-sensitive and -resistant murine leukemia cell lines in vivo.[38,40] Moreover, a recent study in human cell lines that are highly resistant to cisplatin and cross-resistant to carboplatin also showed oxaliplatin to have a different spectrum of activity than cisplatin and low cross-resistance.[18] Specifically, oxaliplatin was active against six of eight colon cancer cell lines in the National Cancer Institute's Anticancer Drug Screen Panel that were resistant to cisplatin and carboplatin.[18]

These preclinical observations of the antitumor activity of oxaliplatin have been confirmed in phase I studies in more than 90 patients with a variety of histologically confirmed, advanced malignancies irresponsive to conventional chemotherapy or for which no beneficial therapy is available.[41-43] These studies also established that the dose-limiting toxicity of oxaliplatin is sensitive peripheral neuropathy and that effective doses of oxaliplatin, unlike those of cisplatin or carboplatin, are associated with minimal hematologic toxicity, minimal grade 3 to 4 gastrointestinal toxicity, and the absence of renal and auditory toxicity.[39,41-43] These encouraging results, which clearly differentiated oxaliplatin from cisplatin and carboplatin, led to the design of phase II trials to evaluate the safety and efficacy of oxaliplatin in patients with a variety of advanced cancers.

It should be stressed that the clinical evaluation of oxaliplatin in patients with advanced colorectal cancer has been unorthodox in terms of its methodologic sequence. Several hundred patients received oxaliplatin in combination with 5-FU plus FA administered as a 5-day chronomodulated infusion, as developed and recommended by Lévi et al.[10] This combination was chosen following the demonstration of its synergistic activity in vitro and in vivo against murine leukemia cell lines.[10,39] Subsequently, oxaliplatin given at the currently recommended dose and schedule as a 2-hour infusion was also combined with 5-FU/FA in a continuous, nonchronomodulated, 48-hour infusional delivery schedule, as published by de Gramont et al.[9,44,45] After several hundred patients with advanced colorectal cancer had been treated with one of these oxaliplatin–5-FU/FA combinations, it became necessary to determine the real single-agent activity of oxaliplatin in patients with advanced colorectal cancer. Moreover, the single-agent phase II trials in patients with advanced colorectal cancer who had received prior 5-FU–based treatment preceded the trials in previously untreated patients with advanced colorectal cancer. For the sake of clarity and ease of understanding, this report and those by Extra et al and Bleiberg and de Gramont elsewhere (see pp 13-22 and 32-39, respectively) in this supplement present the clinical data for oxaliplatin in an orthodox methodologic sequence. The rest of this report is devoted to a presentation of the phase II trials of oxaliplatin administered as a single agent to patients with advanced colorectal cancer.

PHASE II CLINICAL TRIALS OF OXALIPLATIN AS A SINGLE AGENT

The safety and efficacy of oxaliplatin monotherapy in patients with advanced colorectal cancer has been evaluated in five phase II trials, two including 63 previously untreated patients and three including 139 patients with metastatic disease previously treated with and mostly refractory to 5-FU.[46-49]

Previously Untreated Patients

A multicenter phase II trial of the French Fédération Nationale des Centres de Lutte Contre le Cancer conducted by Becouarn et al[46] evaluated the single-agent activity of oxaliplatin in previously untreated patients with metastatic colorectal cancer. Oxaliplatin was administered at a dosage of 130 mg/m^2/d, infused over 2 hours every 3 weeks. In this study, all clinical and radiologic data were reviewed by an external expert panel, and their assessment was considered to be definitive. Of 39 patients entered in the noncomparative

trial when enrollment closed in October 1996, one patient was excluded for having a second cancer and did not receive oxaliplatin therapy. The remaining 38 patients were evaluable for toxicity, and 37 of these patients were evaluable for efficacy at the final analysis, completed in September 1997. An interim analysis of 27 patients has been presented elsewhere.[46] The median age of the total cohort was 67 years (range, 45 to 74 years), slightly more than half the patients were male, and all but one patient had a WHO performance status of 0 or 1. Colon primary tumors outnumbered rectal cancers by a ratio of 30:8. These patient and disease characteristics are summarized in Table 2. One hundred seventy-five cycles (85% of the total 207 administered; median, 5.5 cycles per patient; range, one to nine cycles) with a median cumulative oxaliplatin dose of 670 mg/m^2 (range, 130 to 1,110 mg/m^2) evaluated for toxicity were well tolerated, with peripheral neurotoxicity grade 3, as measured by the Oxaliplatin Neurotoxicity Specific Scale, observed in 13% of patients during 6.3% of cycles. Among the 37 patients evaluated for response (WHO criteria), there were nine objective responses (Table 3); all nine were partial responses confirmed by third-party radiologic review, for an overall response rate of 24.3% (95% confidence interval [CI], 11.8% to 41.2%). Fifteen patients (40.5%) had disease stabilization, and 13 patients (35.2%) had disease progression. The median duration of response was 7 months, the median progression-free survival was 4 months (95% CI, 2 to 6 months), and the median overall survival time was 13 months (95% CI, 10 to 18 months). Thus, this trial shows that oxaliplatin is an active and well-tolerated single agent in previously untreated patients with advanced colorectal cancer.

Table 2. Characteristics of Previously Untreated Patients Receiving Single-Agent Oxaliplatin as First-Line Therapy

Characteristic	Becouarn et al[46]	Diaz-Rubio et al[47]
No. of patients enrolled	39	25
No. of patients evaluable		
For toxicity	38	25
For efficacy	37	25
Age (yr)		
Median	67	60
Range	45-74	38-70
Gender		
Male	21	17
Female	17	8
WHO performance status		
0	22	12
1	15	13
2	1	
Site of primary tumor		
Colon	30	14
Rectum	8	11
No. of metastatic sites		
1	21	11
2	12	6
≥3	5	8
Metastatic sites		
Liver	30	18
Lung	13	2
Other	17	5

Similar results had been obtained in an earlier multicenter phase II trial conducted by Diaz-Rubio et al[47] at several treatment centers in Italy and Spain. In that study, 25 patients with metastatic colorectal carcinoma were enrolled from July 1994 to November 1995. An intermediate analysis of 14 patients has been described.[47] Oxaliplatin was administered as a 2-hour infusion of 130 mg/m^2/d every 3 weeks. The patient characteristics of this trial are summarized in Table 2; there were minor differences in patient profiles between this and the previous trial (eg, more male patients, lower median age). One hundred twenty-three treatment cycles were administered (median, five cycles per patient; range, one to nine cycles), with a median cumulative oxaliplatin dose of 650 mg/m^2 (range, 130 to 1,170 mg/m^2). Although mild peripheral neurologic symptoms were frequent, occurring in 92% of patients during 82% of cycles, no patient developed WHO grades 3 to 4 peripheral neurotoxicity. The efficacy results are summarized in Table 3. There were three confirmed partial responses after external radiologic review, for an overall response rate of 12%. The median duration of response was 6 months, the median progression-free survival was 4 months (95% CI, 2 to 7 months), and the median overall survival time was 14.5 months (95% CI, 10 to 20 months). As in the previous trial, this study confirmed the safety and efficacy of single-agent oxaliplatin as first-line chemotherapy for previously untreated patients with advanced colorectal cancer. Twelve objective responses in 62 evaluable patients, for an overall response rate of 18% (95% CI, 9% to 30%), con-

Table 3. Antitumor Activity of Single-Agent Oxaliplatin in Patients With Advanced Colorectal Cancer

	No. of Patients in Study (Enrolled/ Evaluated)	Oxaliplatin Therapy		Overall Response Rate, % (95% CI)	Stable Disease Rate (%)	Median Duration of Response (mo)	Median Progression-Free Survival (mo)	Median Overall Survival (mo)
		Median No. of Cycles per Patient (Range)	Median Cumulative Dose, mg/m^2 (Range)					
First-line therapy								
Becouarn et al[46]	39/37	5.5 (1-9)	670 (130-1,110)	24.3 (11.8-41.2)	40.5	7	4 (2-6)	13 (10-18)
Diaz-Rubio et al[47]	25/25	5 (1-9)	650 (130-1,170)	12 (NA)	NA	6 (4-9)	4 (2-7)	14.5 (10-20)
Total	64/62			18 (9-30)	—	6-7	4	13-14.5
Second-line therapy								
Machover et al[48]	58/55	5 (1-16)	650 (130-1,990)	11 (0.03-0.19)	42	NA (5-13)	NA	8.2 (9-18.5)
Diaz-Rubio (reported by Machover et al[48])	51/51	3 (2-8)	390 (260-1,010)	10 (0.017-0.18)	31	NA (4-9)	NA	NA (4+-12)
Levi et al[49]	30/29	3 (2-9)	500 (275-1,550)	10	24	5	5	10
Total	139/135	3-5		10.4	34	—	—	8.2-10

Abbreviation: NA, not available.

firm that the single-agent activity of oxaliplatin is comparable to that of other anticancer agents considered active.

Previously Treated Patients

The safety and efficacy of monotherapy with oxaliplatin were also evaluated in patients with advanced colorectal carcinoma refractory to previous treatment with 5-FU. One multicenter phase II study conducted by Machover et al[48] enrolled 58 patients (36 men and 22 women aged 39 to 75 years) with previously diagnosed metastatic colorectal carcinoma and confirmed tumor progression during prior treatment with a 5-FU–containing regimen. The colon was the site of the primary tumor in two thirds of the patients, 83% had liver metastases, and the Eastern Cooperative Oncology Group performance status was 0 to 1 in 86%. These and other relevant patient and disease characteristics are summarized in Table 4. Oxaliplatin therapy consisted of 130 mg/m^2/d administered as a 2-hour infusion every 3 weeks. Three hundred fourteen cycles (median, five cycles per patient; range, one to 16 cycles) were evaluated for toxicity; the median cumulative dose of oxaliplatin given during the study was 650 mg/m^2 (range, 130 to 1,990 mg/m^2). Sensory peripheral neuropathy was observed in 98% of the patients; as measured by the Neurotoxicity Specific Scale, 23% had grade 3 and 8% had grade 4. A correlation was found between increasing incidence and severity of the neuropathy and increasing cumulative doses of oxaliplatin. Despite the high rate of protracted dysesthesia and minor functional impairment (grades 3 and 4 on the Neurotoxicity Specific Scale), all patients who had long-term neurologic follow-up had disappearance or partial regression of neurotoxic symptoms during follow-up. During a median follow-up of 7 months (range, 1 to 18.5 months), 55 patients were evaluated for efficacy. Of these, six patients attained a partial response, for an overall response rate of 11% (95% CI, 0.03% to 0.19%); 23 patients (42%) had disease stabilization; and 26 (47%) had disease progression (Table 3). Time required to achieve a response was 6 weeks, and times to disease progression in the responders were 5, 5, 6, 6, 6+, and 13 months. Median survival time for the 58 patients was 8.2 months, and survival times of the responders were 9, 9+, 12, 14.5, 15, and 18.5 months.

Between May 1993 and June 1994, a second European multicenter phase II trial conducted by Diaz-Rubio enrolled 51 patients, 32 men and 19 women, ages 39 to 75. The results of this trial were published in a single report with the results of a trial conducted by Machover et al.[48] As shown in Table 4, these patients had similar characteristics to those in the prior study, with the colon the primary tumor site in more than half of the patients, liver metastases in 78%, a WHO perfor-

Table 4. Characteristics of Previously Treated Patients Receiving Single-Agent Oxaliplatin as Second-Line Therapy

Characteristic	Machover et al[45]	Diaz-Rubio (Reported by Machover et al[46])	Lévi et al[49]
No. of patients enrolled	58	51	30
No. of patients evaluable			
For toxicity	58	51	29
For efficacy	55	51	29
Age (yr)			
Median	62	61	60
Range	39-75	39-75	33-75
Gender			
Male	36	32	24
Female	22	19	5
Performance status	ECOG criteria	WHO criteria	WHO criteria
	0-1: 50 (86%)	0: 21 (41%)	0-1: 27 (93%)
	2: 7	1: 24 (47%)	2: 2
	3: 1	2: 6	
Site of primary tumor			
Colon	38 (66%)	28 (55%)	19 (66%)
Rectum	20 (34%)	23 (45%)	10 (34%)
No. of metastatic sites			
1	40 (69%)	31 (61%)	16 (55%)
2	17	17	10
≥3	1	3	3
Metastatic sites			
Liver	48 (83%)	40 (78%)	27 (93%)
Lung	NA	NA	7
Other	10	11	9

Abbreviations: NA, not available; ECOG, Eastern Cooperative Oncology Group.

mance status of 0 to 1 in 88% of patients, and all 51 patients evaluable. Oxaliplatin therapy was again 130 mg/m^2/d, administered as a 2-hour infusion every 3 weeks. Two hundred three cycles (median, three cycles per patient; range, two to eight cycles) were delivered and evaluated; the median cumulative dose of oxaliplatin was 390 mg/m^2 (range, 260 to 1,010 mg/m^2). Sensory peripheral neuropathy was observed in 96% of the patients, with grade 3 in 14% and grade 4 in 4% (specific scale). As in the preceding trial, the incidence and severity of peripheral neuropathy were correlated with increasing cumulative dose, and neurotoxic symptoms disappeared or were attenuated after discontinuation of oxaliplatin; follow-up was too short, however, for precise evaluation of neurotoxic regression. With a median follow-up of 4.5 months (range, 1 to 13 months), all 51 patients were evaluated for efficacy. A partial response was attained in five patients, for an overall response rate of 10% (95% CI, 0.017% to 0.18%); 16 patients (31%) had no change and 30 (59%) had disease progression (Table 3). In the responders, the times to disease progression were 4, 4, 4.5+, 6, and 9 months, and the survival times were 4+, 5.5, 6+, 7+, and 12 months.

A third multicenter phase II trial conducted by Lévi et al[49] also evaluated oxaliplatin monotherapy in patients with metastatic colorectal cancer. Thirty patients entered the trial between May 1990 and May 1991. As shown in Table 4, 29 patients were evaluable (24 men and five women with a median age of 60 years [range, 33 to 75 years]). The colon was the primary tumor site in two thirds of the patients, 93% had liver metastases, and 93% had a WHO performance status of 0 to 1. Of the 29 evaluable patients, 25 (86%) had failed previous chemotherapy. Oxaliplatin was administered by chronomodulated, continuous 24-hour infusion (peak at 4:00 PM) of 30 mg/m^2/d for 5 days (total dose, 150 mg/m^2), repeated every 3 weeks (16-day interval); in the absence of toxicity

grade ≥3 after the first cycle, daily doses were escalated to 35 mg/m^2 for the second cycle (175 mg/m^2) and 40 mg/m^2 for the third cycle (200 mg/m^2). One hundred eight cycles (median, three cycles per patient; range, two to nine cycles) were administered, with a median total dose of 500 mg/m^2 (range, 275 to 1,550 mg/m^2). Four patients withdrew because of toxicity, one because of grades 3 and 4 diarrhea after the first and second cycles, respectively, and three because of sensitive peripheral neuropathy after four or six cycles. As in the first two studies, the incidence and severity of peripheral-sensitive neuropathy correlated with the cumulative dose of oxaliplatin; moreover, neurotoxic symptoms frequently regressed during treatment intervals or responded to course interruption with reintroduction at a lower dosage. All 29 patients were evaluated for efficacy (Table 3). Objective responses were documented after three cycles in three patients (response rate, 10%); all three patients had liver metastases of colon cancer and had prior disease progression while receiving 5-FU plus FA. The disease was stabilized in seven patients (24%) for 3.2 to 4.2 months and progressed in the remaining 19 patients (66%). The median progression-free survival was 20 weeks, and the estimated median overall survival was 40 weeks.

Although modest, the consistent overall response rate of at least 10% obtained with single-agent oxaliplatin in 5-FU–refractory patients in these trials (Table 3) contrasts sharply with the 0% and 3% overall response rates obtained, respectively, with single-agent cisplatin and carboplatin (Table 1). Moreover, the median number of oxaliplatin cycles administered confirms the high stabilization rates (24% to 42%) observed with single-agent oxaliplatin, establishing the antitumor activity and therapeutic advantage of this agent for patients with advanced colorectal cancer refractory to 5-FU.

CONCLUSION

These five phase II clinical trials have shown that oxaliplatin administered as a single agent has clinical antitumor effects against metastatic colorectal cancer, both in previously untreated patients and in heavily pretreated patients refractory to 5-FU. The objective response rate achieved with first-line therapy (18%) was highly reproducible, as was that yielded by second-line therapy (10%). Moreover, these rates were achieved within acceptable limits of tolerability and only moderate toxicity. These response rates, while modest, are similar to those obtained with single agents such as 5-FU in previously untreated patients and in patients resistant to 5-FU.[48-50]

Despite the antitumor activity of oxaliplatin in patients with advanced colorectal cancer, single-agent use of oxaliplatin is not recommended as standard therapy except in patients with dihydropyrimidine dehydrogenase deficiency, which is associated with increased risk of very severe or lethal 5-FU toxicity, or in those with cardiotoxicity from 5-FU.[51]

Many in vitro and in vivo experimental data have suggested that the action of oxaliplatin combined with 5-FU is not merely additive but synergistic.[39,52] For clinical confirmation of this effect, the majority of patients who received oxaliplatin in clinical trials were treated with oxaliplatin in combination with 5-FU, as discussed in the report by Bleiberg and de Gramont elsewhere in this supplement (see pp 32-39).

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Oxaliplatin Plus 5-Fluorouracil: Clinical Experience in Patients With Advanced Colorectal Cancer

Harry Bleiberg and Aimery de Gramont

Oxaliplatin was first introduced to the clinical setting as a combination therapy with 5-fluorouracil/folinic acid (5-FU/FA) in an attempt to improve the response rate obtained with 5-FU/FA against colorectal cancer. To dispel the impression that the improvements observed in objective response were somehow due to the chronomodulated regimen used, oxaliplatin was also tested in constant-rate infusion schedules and in regimens using bolus administration followed by 5-FU/FA infusion. The most current data comparing chronomodulated infusion and constant-rate infusion in untreated patients show a lower objective response rate for the latter (51% v 29%), but comparable median progression-free survival and median survival (9.8 months and 15.9 months v 7.9 months and 16.9 months, respectively). The first trials using constant-rate therapy included pretreated patients with metastatic colorectal cancer, most of whom were refractory to 5-FU. In these studies, conducted using two different regimens or variations of them, objective response rates ≤46% were obtained. The addition of oxaliplatin to 5-FU/FA in controlled, randomized phase III trials has resulted in a twofold or greater increase in objective response rate and a 3-month gain in time to progression, with survival differences blurred by crossover effect. Compassionate-use programs that included many heavily pretreated relapsing patients reported response rates of 15% to 25%, confirming the value of the oxaliplatin–5-FU/FA regimen and suggesting that oxaliplatin may act synergistically with 5-FU.

Semin Oncol 25 (suppl 5):32–39.

SINCE its introduction into clinical practice 40 years ago, 5-fluorouracil (5-FU) has been the standard chemotherapeutic agent for the treatment of patients with metastatic colorectal carcinoma.[1-3] However, response rates with single-agent administration of 5-FU bolus rarely exceed 15%. There have been numerous attempts to increase the antiproliferative activity of this cytotoxic agent.[1-8] The various approaches have included modifications of the dosage and administration schedules of 5-FU, biochemical modulation of 5-FU with folinic acid (FA) or other modulators, and combination of 5-FU with other cytotoxic agents such as cisplatin.[1-8] Some of these strategies have increased the toxicity of this therapy, however, and the best response rates are above 30%. Consequently, new chemotherapeutic agents with potential clinical significance are being actively researched.[1-8]

Oxaliplatin, a new third-generation cisplatin analogue in the 1,2-diaminocyclohexane family of platinum compounds, has recently been developed for clinical use in France.[9,10] Preclinical studies have shown that the antitumor activity of this agent is superior to that of cisplatin in vitro and in vivo against murine leukemia, in vivo against several murine solid tumors, and in vitro against human colon carcinoma cell lines.[10-14] Other preclinical observations suggest that oxaliplatin has synergistic antitumor activity with 5-FU in vitro and in vivo in murine leukemia cell cultures transplanted into mice and in human colonic xenografts either sensitive or resistant to 5-FU.[15,16]

More than 2,000 patients have received oxaliplatin in clinical trials, over 1,400 of them as treatment of metastatic colorectal cancer. In some trials, oxaliplatin was administered as a single agent (see the report by Becouarn and Rougier elsewhere in this supplement [pp 23-31]). In other trials, oxaliplatin was administered in combination with 5-FU modulated by FA and was delivered either by constant-rate infusion or via chronomodulated therapy. This report presents the results achieved with constant-rate infusion of oxaliplatin. Chronomodulated infusion results are presented in Tables 1 to 3 as a point of comparison, but are more extensively discussed in the article by Bismuth and Adam elsewhere in this supplement (see pp 40-46).

ANTITUMOR ACTIVITY IN PREVIOUSLY UNTREATED PATIENTS

Oxaliplatin combined with 5-FU/FA has been evaluated in 614 previously untreated patients with metastatic colorectal cancer: 136 patients in two phase II trials and 478 patients in three phase III trials.[6,17-20]

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Phase II Trials

Two phase II studies evaluated oxaliplatin combined with 5-FU/FA in chemotherapy-naive patients. In both trials, oxaliplatin was delivered as a chronomodulated infusion (see Bismuth and Adam, pp 40-46).

Phase III Trials

The first phase III trial to evaluate the clinical antitumor activity of oxaliplatin combined with 5-FU/FA compared chronomodulated and constant-rate delivery schedules in 92 consecutive patients with metastatic colorectal cancer enrolled at seven European cancer centers from May 1990 to May 1991.[18] Treatment consisted of continuous intravenous (IV) infusion of oxaliplatin 20 mg/m^2/d, 5-FU 600 mg/m^2/d, and FA 300 mg/m^2/d for 5 days, repeated every 21 days; drug delivery was kept constant in 47 patients (51%) and chronomodulated in 45 (49%). The patient characteristics for each treatment arm are summarized in Table 1. Overall, 47 patients (51%) were men, the median age was 60 years (range, 31 to 73 years), and 83 (90%) had a World Health Organization performance status ≤1. The colon was the primary tumor site in 64 patients (70%), 43 patients (47%) had two or more metastatic sites, and 80 patients (87%) had liver metastases.

Of the 707 cycles administered, 675 to 686 (95% to 97%) were evaluated for various toxicities. The most frequent dose-limiting toxicity was stomatitis, with severe toxicities (grade 3 or 4) occurring 8.7 times more frequently in patients receiving nonchronomodulated treatment. In general, severe (grade 3 or 4) diarrhea, nausea or vomiting, and skin toxicity occurred in fewer than 5% of cycles. There was no hematologic toxicity or peripheral sensitive neuropathy above grade 2. As summarized in Table 2, 15 of 47 patients (32%) receiving

Table 1. Characteristics of Previously Untreated Patients in Oxaliplatin Plus 5-FU/FA Phase III Trials With Chronomodulated Delivery

Characteristic	Levi et al[18] (%)		Levi et al[21] (%)		Giacchetti et al[20] (%)	
	Constant Rate	Chronomodulated	Constant Rate	Chronomodulated	Without Oxaliplatin	With Oxaliplatin
No. of patients enrolled	47	45	93	93	100	100
Age (yr)						
Median	60	60	61	61	–	–
Range	34-73	31-73	29-75	22-75	–	–
Gender						
Male	27 (57)	20 (44)	60 (65)	52 (56)	–	–
Female	20 (43)	25 (56)	33 (35)	41 (44)	–	–
WHO performance status						
0	14 (30)	19 (42)	50 (54)	49 (53)	66 (66)	69 (69)
1	27 (57)	23 (51)	34 (37)	30 (32)	27 (27)	20 (20)
2	6 (13)	3 (7)			7 (7)	11 (11)
2-3			9 (10)	14 (15)		
Site of primary tumor						
Colon	30 (64)	34 (76)	66 (71)	63 (68)	77 (77)	66 (66)
Rectum	17 (36)	11 (24)	27 (29)	30 (32)	23 (23)	34 (34)
No. of metastatic sites						
1	27 (57)	22 (49)	55 (59)	56 (60)	46 (46)	50 (50)
≥2	20 (43)	23 (51)	38 (41)	37 (40)	52 (52)	50 (50)
Metastatic sites						
Liver	40 (85)	40 (89)	75 (81)	76 (82)	49 (49)	50 (50)
Lung	11 (23)	20 (44)	38 (41)	29 (31)	–	–
Lymph nodes			7 (8)	11 (12)	–	–
Peritoneum	15 (32)	11 (24)	13 (14)	11 (12)	–	–
Other	5 (11)	3 (7)	2 (2)	10 (11)	–	–

Abbreviation: WHO, World Health Organization.

Table 2. Antitumor Activity of Oxaliplatin Plus 5-Fluorouracil and Folinic Acid in Previously Untreated Patients With Metastatic Colorectal Cancer

	No. of Patients Evaluated	Dosage and Schedule (mg/m²), Constant Rate or Chronomodulated			Objective Response Rate (%)	Complete Response Rate (%)	Stable Disease Rate (%)	Median Progression-Free Survival (mo)	Median Survival Time (mo)
		Oxaliplatin	5-Fluorouracil	Folinic Acid					
Phase II trials									
Lévi et al[8]	46	25 × 5 d every 3 wk, chrono	700 × 5 d every 3 wk, chrono	300 × 5 d every 3 wk, chrono	59	11	30	11	15
Lévi et al[17]	90	25 × 4 d every 2 wk, chrono	700-1,000 × 4 d every 2 wk, chrono	300 × 4 d every 2 wk, chrono	67	3	—	—	19
Phase III trials									
Lévi et al[18]	47	20 × 5 d every 3 wk, constant	600 × 5 d every 3 wk, constant	300 × 5 d every 3 wk, constant	32	4	45	8	14.9
	45	20 × 5 d every 3 wk, chrono	600 × 5 d every 3 wk, chrono	300 × 5 d every 3 wk, chrono	53	7	36	11	19
Lévi et al[21]	93	25 × 5 d every 3 wk, constant	600 × 5 d every 3 wk, constant	300 × 5 d every 3 wk, constant	29	3	—	7.9	16.9
	93	25 × 5 d every 3 wk, chrono	600 × 5 d every 3 wk, chrono	300 × 5 d every 3 wk, chrono	51	5	—	9.8	15.9
Giacchetti et al[20]	100	125 × 1 d every 3 wk, constant	700 × 5 d every 3 wk, chrono	300 × 5 d every 3 wk, chrono	34*	—	—	7.7	Not reached at 12 mo
	100	None	700 × 5 d every 3 wk, chrono	300 × 5 d every 3 wk, chrono	12*	—	—	4.6	Not reached at 12 mo

* Response rate confirmed at 9 weeks by external review.
Adapted and reprinted with kind permission from Kluwer Academic Publishers.[31]

flat-rate, continuous infusion had an objective response, which was complete in two patients (4%) and partial in 13 (28%); 21 patients (45%) had stable disease and 10 patients (21%) had disease progression. The median progression-free survival was 8 months, and the median survival was 14.9 months; overall, 18 patients (20%) were alive at a median follow-up of 30 months. This trial was prematurely terminated, however, because of potential neutralization of oxaliplatin by the basic 5-FU solution in the flat-rate infusion arm.

A second multicenter phase III trial used the same protocol but higher doses to compare chronomodulated and constant-rate delivery schedules of oxaliplatin combined with 5-FU/FA in 186 previously untreated patients with metastatic colorectal cancer enrolled from July 1991 to February 1993.[21] Treatment consisted of a 5-day continuous IV infusion of oxaliplatin 25 mg/m²/d, 5-FU 600 mg/m²/d, and FA 300 mg/m²/d, with patients randomized to receive, on an outpatient basis, either flat-rate delivery (n = 93) or chronomodulated delivery (n = 93). The patient characteristics of the two treatment arms are summarized in Table 1.

Of 1,301 cycles, 1,259 (97%) were evaluated for toxicity. In the constant-rate arm, 51% of patients required withdrawal for toxic effects and 31% required hospitalization for grade 4 gastrointestinal toxicity or peripheral sensitive neuropathy. An objective response was achieved in 27 patients receiving flat-rate delivery, for a response rate of 29% (95% confidence interval [CI], 19.6 to 38.4); there were three complete responses (Table 2). The median progression-free survival was 7.9 months, and the median survival was 16.9 months.

A third and most important recently reported phase III study investigated the addition of a constant-rate infusion of oxaliplatin to the chronomodulated delivery of 5-FU/FA in 200 patients with previously untreated metastatic colorectal cancer.[20] Patients were enrolled at 15 cancer centers from June 1994 to March 1996 and were randomized to receive chronomodulated delivery of 5-FU 700 mg/m²/d plus FA 300 mg/m²/d, each for 5 days, with or without a 6-hour flat-rate infusion of oxaliplatin 125 mg/m² on day 1, and repeated every 3 weeks. There were 100 patients assigned to each treatment arm. The main patient characteristics are listed in Table 1.

The incidence of grades 3 and 4 toxicity during

728 cycles without oxaliplatin was 5% for diarrhea, 4% for mucositis, and 2% for nausea and vomiting; during 774 cycles with oxaliplatin, the incidence was 43% for diarrhea, 10% for mucositis, 25% for nausea and vomiting, and 13% for specific scale grade 4 peripheral sensitive neuropathy. As shown in Table 2, the objective response rate at 9 weeks was 12% (95% CI, 6 to 20) without oxaliplatin and 34% (95% CI, 24 to 44) with oxaliplatin ($P < .001$). Patients in the oxaliplatin arm achieved better median progression-free survival (8.9 months *v* 5.2 months) and comparable median survival (17.6 months *v* 19.4 months).[22] Subsequently, 57 of 70 patients in the 5-FU/FA arm without oxaliplatin received second-line chemotherapy with oxaliplatin plus 5-FU/FA. Oxaliplatin was delivered by short infusion in 27 patients and was chronomodulated in 30.[22] A partial response was achieved in 10 patients; 32 patients had stable disease. Disease was controlled in 42 of 57 patients (74%), including 16 of 21 patients (76%) who were refractory to 5-FU.[22]

A recently completed, randomized, multicenter European trial of LV5-FU2 ± oxaliplatin enrolled 210 patients in each arm. The results will be presented at the 1998 American Society of Clinical Oncology meeting, and are expected to confirm the efficacy of oxaliplatin in optimizing the response to 5-FU/FA in previously untreated patients.

ANTITUMOR ACTIVITY IN PREVIOUSLY TREATED PATIENTS

Oxaliplatin in combination with 5-FU/FA also has been evaluated in 1,106 previously treated patients with refractory metastatic colorectal cancer. Eight prospective phase II trials included 385 of these patients. The remaining 721 patients were evaluated in extended-access, compassionate-use programs, which have been thoroughly and completely assessed by retrospective analyses.[2,6,23-29]

Constant-Rate Infusion Studies

The feasibility of high-dose, constant-rate, continuous infusion of oxaliplatin plus 5-FU/FA in 2-week cycles was evaluated over 137 cycles in a study of 13 patients with progression of pretreated colorectal cancer.[23] Treatment consisted of oxaliplatin 130 mg/m^2/d over 2 hours on day 1 of every other cycle, plus 5-FU 2,000 mg/m^2/d over 24 hours after FA 500 mg/m^2/d over 2 hours on days 1 and 2 of every cycle (FOLFOX-1). With this regimen, 31% of patients experienced an objective response; seven patients (54%) experienced grade 3 or 4 toxicity (Table 3). To reduce toxicity and to take full advantage of synergistic effects with 5-FU, oxaliplatin was administered at 100 mg/m^2/d on day 1 of every cycle and the dose of 5-FU was reduced to 1,500 mg/m^2/d for two cycles, then increased to 2,000 mg/m^2/d if there was no toxicity higher than grade 2 (FOLFOX-2).

Use of the FOLFOX-2 regimen was expanded into a full phase II study in 46 patients enrolled from February 1993 to January 1995.[2] Patient characteristics were similar to those of the earlier study: 63% of patients were men, the median age was 59.4 years, the colon was the primary tumor site in 52% of patients, liver and lung metastases were present in 85% and 28% of patients, respectively, 67% of patients had only one metastatic site, and 89% of patients had a World Health Organization performance status ≤1.

During a median of 10 cycles per patient, the dose-limiting toxicities were grade 3 or 4 neutropenia in 18 patients (39%) and grade 2 or 3 peripheral neuropathy in 20 patients (33%). The objective response rate was 46% (95% CI, 31 to 60), with one complete response that lasted 8 months and 20 partial responses that had a median duration of 8.5 months. Twenty-one patients (46%) had stable disease and three (7%) had disease progression (Table 3). In a subgroup of 22 patients who had been refractory to the same 5-FU/FA schedule without oxaliplatin, 10 patients (45%) achieved a partial response (95% CI, 24 to 67) and 10 (45%) had stable disease. Moreover, the response rate was 44% in patients with liver metastases and 46% in those with lung metastases.

The FOLFOX-3 regimen was introduced to further decrease the toxicity of the combination (Table 3).[30] With this regimen, the oxaliplatin dose was reduced to 85 mg/m^2 with FA at 500 mg/m^2 on days 1 and 2 and 5-FU administered as a 3,000 mg/m^2 48-hour infusion starting on day 2. Patients with ≤grade 2 toxicity after two cycles received 4,000 mg/m^2 5-FU. Thirty patients refractory to 5-FU were treated biweekly with FOLFOX-3 until progression. Six (20%) achieved a partial response and 15 (50%) had stable disease. Grade 3-4 toxicity was limited to eight patients (27%).

Two additional 2-week regimens of oxaliplatin plus 5-FU/FA were evaluated after disease progres-

Table 3. Antitumor Activity of Oxaliplatin Plus 5-Fluorouracil and Folinic Acid in Previously Treated Patients With Metastatic Colorectal Cancer

	No. of Patients Evaluated	Dosage and Schedule (mg/m²)			Objective Response Rate (%)	Complete Response Rate (%)	Stable Disease Rate (%)	Median Progression-Free Survival (mo)	Median Survival Time (mo)
		Oxaliplatin	5-Fluorouracil	Folinic Acid					
Flat-rate delivery									
FOLFOX-1, de Gramont et al[23]	13	130 × 1 d every 4 wk (over 2 hr)	1,500-2,000 × 2 d every 2 wk (over 24 hr)	500 × 2 d every 2 wk (over 2 hr)	31	0	38	—	—
FOLFOX-2, de Gramont et al[2]	46	100 × 1 d every 2 wk (over 2 hr)	1,500-2,000 × 2 d every 2 wk (over 24 hr)	500 × 2 d every 2 wk (over 2 hr)	46	1	46	7	17
FOLFOX-3, de Gramont et al[10]	30	85 × 1 d every 2 wk (over 2 hr)	1,500-2,000 × 2 d every 2 wk (over 48 hr)	500 × 2 d every 2 wk (over 2 hr)	20	0	50	6	10
FOLFOX-3,[a] Andre et al[24]	48	85 × 1 d every 2 wk (over 2 hr)	1,500 × 2 d every 2 wk (over 48 hr)	500 × 2 d every 2 wk (over 2 hr)	25	0	—	—	—
FOLFOX-4,[a] Andre et al[24]	36	85 × 1 d every 2 wk (over 2 hr)	1,000 × 2 d every 2 wk (over 24 hr)	200 × 2 d every 2 wk (over 2 hr)	25	0	—	—	—
Gerard et al[25]	34	130 × 1 d every 3 wk	2,600 × 2 d (over 24 hr) every 3 wk (d 1 & 8)	500 × 2 d every 3 wk (d 1 & 8)	24	0	18	—	7
Meyer et al[31]	38	130 × 1 d every 3 wk (over 2 hr)	1,300 every 3 wk	400 every 3 wk	36	0	36	5.5	7.6
Chronotherapy									
Levi et al[8]	42	25 × 5 d every 3 wk	700 × 5 d every 3 wk	300 × 5 d every 3 wk	55	2	40	10	13
Brienza et al[26]	57	25 × 4 d every 2 wk	700 × 4 d every 2 wk	300 × 4 d every 2 wk	38	4	—	10	13
Bertheault-Cvitkovic et al[27]	37	20-25 × 4 d every 2 wk	700 × 4 d every 2 wk	300 × 4 d every 2 wk	40	3	51	10.3	16.9
Garufi et al[28]	25	20-25 × 4 d every 2 wk or × 5 d every 3 wk	700-1,000 × 4 d every 2 wk or × 5 d every 3 wk	300 × 4 d every 2 wk or × 5 d every 3 wk	29	0	50	5.8	12

[a] Data updated for presentation at the European Cancer Conference, Hamburg 1997 (ECCO 9, abstr 738).

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sion on 5-FU/FA in 99 patients with metastatic colorectal cancer enrolled in an ongoing multicenter study from October 1995 to November 1996.[24] Oxaliplatin 85 mg/m^2/d over 2 hours on day 1 of each cycle was added either to 5-FU 1,500 mg/m^2/d plus FA 500 mg/m^2/d on days 1 and 2 (FOLFOX-3) or to 5-FU 400 mg/m^2/d bolus and 600 mg/m^2/d continuous IV infusion over 22 hours plus FA 200 mg/m^2/d over 2 hours on days 1 and 2 of every cycle (FOLFOX-4), and repeated every 2 weeks. Eighty-four patients were evaluated in an updated interim analysis from September 1997 (Table 3). Overall, an objective response rate of 25% was achieved. Toxicity was assessed in 899 cycles (median, six cycles per patient; some received 16+ cycles), with the median dose of oxaliplatin at 510 mg/m^2 (range, 255 to 1,360+ mg/m^2). The results confirm previous reports of clinical synergy between oxaliplatin and 5-FU.

The highest-dose, flat-rate regimen reported to date was evaluated in 34 patients with advanced colorectal cancer progressing after previous chemotherapy.[25] Every 3 weeks, oxaliplatin 130 mg/m^2 (day 1) plus FA 500 mg/m^2 followed by 5-FU 2,600 mg/m^2 (days 1 and 8) was administered to 16 men and 18 women. The median age was 60 years (range, 34 to 76 years), and the median performance status was 1 (range, 0 to 3). The primary tumor sites were the rectum in 12 patients and the colon in 22; the metastatic sites were the liver in 26 patients, the lung in 12, and the abdominoperitoneal cavity in 11.

The major adverse effect was neurotoxicity, which was mild in 19 patients, moderate in five, severe in two, and required discontinuation in one. Severe diarrhea occurred in four patients, and moderate or severe nausea and vomiting occurred in six and four patients, respectively. The objective response rate was 24%, with eight patients achieving a partial response and six having stable disease (Table 3). The median time to progression was 7+ months (range, 4 to 12 months); the median survival time from diagnosis was 22 months (range, 3 to 63 months) and from initiation of oxaliplatin therapy, 7 months (range, 2 to 47 months).

The synergism observed with the oxaliplatin/5-FU combination was confirmed in a recent trial of 38 patients with advanced colorectal cancer refractory to 5-FU (Table 3).[31] In this study, oxaliplatin (130 mg/m^2) was added as a 2-hour infusion every 3 weeks to an ongoing weekly 5-FU (1,300 mg/m^2)/FA (400 mg/m^2) regimen. After three cycles of oxaliplatin therapy, 14 patients (36%) had a partial response and 14 (36%) had stable disease. The median progression-free survival and median overall survival were 5.5 months and 7.6 months, respectively. In addition, nine patients survived longer than 1 year. The response rates observed in this study appeared higher than would be expected with oxaliplatin alone, suggesting synergism.

New combination regimens (FOLFOX-6, FOLFOX-7) are currently under investigation. These studies take into account factors crucial to improving oxaliplatin-based therapy. Major concerns include immediate hematologic toxicity and cumulative neurotoxicity, which govern the dose of 5-FU used and the duration of treatment, respectively. FOLFOX-6 addresses these issues with an increased chemotherapeutic dose (oxaliplatin 100 mg/m^2 plus FA 400 mg/m^2 with 5-FU 2,400 to 3,000 mg/m^2) given over a shorter period of time.

Compassionate-Use Programs

The results obtained in phase II trials have been confirmed in a review of data from 206 patients with advanced colorectal cancer treated with oxaliplatin in a compassionate-use program at 44 European cancer centers from January 1994 to June 1995.[29] Progression on 5-FU/FA schedules was verified in 111 patients; oxaliplatin was then added to the 5-FU/FA schedules, either every 2 weeks at 80 to 100 mg/m^2 per cycle to 49 patients or every 3 weeks at 100 to 135 mg/m^2 per cycle to 62 patients. The objective response rate in 98 evaluable patients was 26% (95% CI, 17.2 to 35.5).

These results also have been confirmed by a retrospective analysis of a French extended-access program in which 490 patients received oxaliplatin for advanced colorectal cancer. In this program, 472 patients received oxaliplatin in combination with 5-FU/FA; of these, 370 proved to be resistant to 5-FU/FA (E. Cvitkovic, personal communication, July 1996). The median dose of oxaliplatin was 126 mg/m^2 per 3-week cycle for 2,702 cycles, and the total cumulative dose was 600 mg/m^2 (range, 70 to 2,300 mg/m^2). The median time to progression was 4.3 months (95% CI, 3.9 to 4.7), and the median survival was 9.7 months (95% CI, 8.5 to 10.8).

In administering 5-FU/FA, both compassionate-use programs incorporated many different regimens with a variety of dosages, schedules, and drug deliv-

ery modalities. Delivery modalities included continuous IV infusion for 5 days, protracted continuous IV infusion, weekly bolus, and bolus for 4 to 5 days; schedules varied from 24 to 48 hours. Despite these differences, however, similar objective response rates were usually observed.

Finally, similar results were also obtained in a small compassionate-use program in which 25 patients received chronomodulated infusions of oxaliplatin plus 5-FU/FA.[28]

CONCLUSION

The clinical trials of oxaliplatin combined with 5-FU/FA in both chemotherapy-naive and previously treated patients with advanced colorectal cancer confirm the observations of in vitro and animal studies that the antitumor activity of oxaliplatin is not merely additive but also synergistic with that of 5-FU. These studies have shown both the effectiveness and the tolerability of the combination of oxaliplatin and 5-FU/FA. Although these results have been substantiated by "real-life scenario" data obtained from large compassionate-use programs, additional trials are needed to determine the most adequate treatment regimens. There are currently two ongoing, large multicenter studies of oxaliplatin in combination with 5-FU/FA as second-line treatment for advanced colorectal cancer. One large phase III trial of oxaliplatin-5-FU/FA as first-line therapy for colorectal cancer completed accrual in mid-1997. Results from this trial are expected to confirm the role of oxaliplatin in treating colorectal cancer.

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Reduction of Nonresectable Liver Metastasis From Colorectal Cancer After Oxaliplatin Chemotherapy

Henri Bismuth and René Adam

Until recently, approximately 30% of patients with resectable hepatic metastases from colorectal cancer survived 5 years after surgery. Additionally, many patients present with unresectable metastases and can look forward only to palliative care. Whereas therapeutic approaches such as cryosurgery appear to improve resectability, a key to resecting hepatic metastases is the ability to shrink the metastatic sites to make them more amenable to surgery. The administration of traditional chemotherapeutic modalities by conventional means or via intra-arterial or portal vein infusion has not provided significant improvements. The recent introduction of the combination oxaliplatin–5-fluorouracil/folinic acid administered as a chronomodulated regimen, however, has provided better response rates with minimal toxicity. Recent results show that the resection of previously unresectable metastases became possible in up to 16% of patients after chemotherapy with a chronomodulated regimen of oxaliplatin plus 5-fluorouracil/folinic acid. Of the patients who had successful resections, 54% and 40% were alive at 3 years and 5 years after surgery, respectively. The results of these studies demonstrate that this new approach can significantly prolong survival for patients with a previously bleak outlook. As a result, new treatment algorithms are evolving, integrating chemotherapeutic and surgical strategies for the treatment of patients with metastatic colorectal cancer.

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SURGERY is considered first-line therapy for colorectal cancer; however, approximately 50% of patients die from recurrence, even though the primary tumor had apparently been resected successfully.[1] Liver metastasis is the most prevalent complication from colorectal cancer and a major contributor to patient mortality due to recurrence.[2] The ability of a colorectal tumor to metastasize appears to be correlated with the expression of various oncoproteins related to the regulation of apoptosis and the cell cycle. The presence of p53 protein in the primary tumor is always indicative of p53 expression in lymph node and liver metastases, and is highly correlated with patient outcome. A recent study demonstrated that the median survival time of patients with tumors positive for p53 overexpression is 21 months, compared with 53.2 months for patients with p53-negative tumors.[3] Overexpression of c-erbB-2 mRNA and/or c-neu oncoprotein is also indicative of the metastatic potential of colorectal tumors, since the presence of overexpressed c-erbB-2 is highly correlated with future development of liver metastases from tumors that have not yet metastasized to lymph nodes.[4] For patients with these genetic alterations, it is essential to apply procedures that have the capability to eradicate not only the primary lesion, but also, when they have occurred, metastases to the lymph nodes and liver.

SURGICAL APPROACH TO LIVER METASTASES

Although surgical resection of hepatic metastases can produce long-term survival with the potential of cure,[5,6] only approximately 30% of patients with resectable disease survive 5 years after surgery.[2,5] In addition, a large number of patients present with hepatic metastases that are considered unresectable because of their size, location, and/or number. Extrahepatic progression is also a major impediment to patients achieving a lasting recovery. Cryosurgery, recently introduced to eliminate colorectal metastases to the liver previously classified as unresectable, has the potential to increase the number of patients who become disease free after surgery.[7] A recent trial of 123 patients demonstrated that 5-year survival rates were higher for patients treated with cryosurgical techniques (44%) than for patients undergoing conventional surgical resection (36%). Additionally, twice as many patients survived 10 years after cryosurgery (19%) than after conventional surgery (8%).[8] Some investigators, however, feel that while promising, the current data do not support the use of cryosurgery other than to tackle unresectable metastases.[9]

CHEMOTHERAPEUTIC APPROACH TO LIVER METASTASES

The management of unresectable disease invariably involves palliative chemotherapy. However,

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a legitimate goal of chemotherapeutic treatment is to favor shrinking of liver metastases to make them more surgically manageable.

Since the early 1990s, the combination of 5-fluorouracil (5-FU) with levamisole has been considered the standard of care in adjuvant chemotherapy. This combination was shown to provide a survival advantage over surgical resection alone for patients with stage III colon cancer.[10,11] This effect, however, did not include patients with stage II disease who demonstrated a decreased rate of relapse but no significant improvement in survival.[12] Folinic acid (FA) is often substituted for levamisole in current combinations on the basis that its association with 5-FU is at least as efficacious as 5-FU plus levamisole and that stage II patients also exhibit improved survival.[13,14] As demonstrated by a meta-analysis of nine randomized trials involving 1,381 patients, however, the response rate to systemic 5-FU plus FA does not exceed 23%, and partial responses are prevalent (20%).[15]

For patients with metastatic disease (stages III or IV), a variety of approaches has been tried in an attempt to reduce the occurrence of liver metastases and to attack those metastases up front. In an effort to increase the amount of cytotoxic drug reaching the liver, infusions have been administered directly into the portal vein or the hepatic artery (a method currently preferred). The benefits derived from these techniques appear, at present, to be minimal.[16,17] A meta-analysis of nine hypothesis-testing trials involving over 3,000 patients treated with portal vein chemotherapy or no further treatment after surgery demonstrated a small improvement of a few percentage points (3.6%; $P = .04$) in absolute survival for patients treated with portal vein chemotherapy versus patients assigned to no further treatment. However, reduction in the incidence of liver metastases in the treatment group (14%) was not significantly different from that of the control group ($P = .2$).[16] The investigators concluded that the small improvement recorded was not statistically secure and that additional trials with many more patients would be required to validate the procedure. In addition, a survival advantage could not be demonstrated when hepatic arterial infusion with 5-fluoro-2′-deoxyuridine was compared with intravenous chemotherapy with either 5-fluoro-2′-deoxyuridine or 5-FU ($P = .14$).[17]

The invasive nature of the catheter and reservoir required to implement arterial infusions is also a source of significant concern, since complications that may involve infections, artery occlusion, gastroduodenal ulcers, and upper gastrointestinal tract symptoms have been recorded.[18] In addition, although this kind of locoregional therapy may have demonstrated some benefit in the reduction of metastases confined to the liver, the possibility of extrahepatic progression, particularly in the lungs, limits the value of this approach and requires that patients selected for this procedure do not have more than one site of metastasis.[19]

Chemotherapeutic regimens have been enhanced with various forms of radiation therapy, including fractionated whole-liver irradiation, followed by a boost dose at the area of dominant disease,[20] and conformal planar radiation therapy focused at the major site of hepatic disease.[21] Although survival rates may improve when such techniques are used, significant concerns remain with respect to the ability to deliver a high enough dose of radiation to obtain a sustainable response without causing severe radiation hepatitis.[22] Another approach to managing patients with unresectable disease has involved cryosurgery with intraoperative chemotherapy; however, the toxicity of 5-FU/FA administered under these conditions is significant.[23] Because of the lackluster progress made using these approaches, some investigators are now seeking to improve the delivery regimen and use combination therapies that offer a prospect for synergistic effectiveness.

Continuous-Infusion Therapy

The concept of using a continuous infusion of 5-FU to treat patients with advanced colorectal cancer was introduced by Seifert et al.[24] This mode of drug delivery provided reported response rates significantly higher than those observed with bolus administration.[25,26] The combination of FA and 5-FU intravenous bolus followed by continuous 5-FU intravenous infusion also provided significantly enhanced response rates of over 50%.[27] Attempts to chronomodulate 5-FU/FA delivery have not been more effective, yielding response rates of up to 40% in chemotherapy-naive patients but only 8% in previously treated patients,[28] emphasizing the problem of resistance building in patients continuously treated with 5-FU.

The development of resistance to 5-FU therapy

is a major impediment to treatment success that has been attributed to high thymidylate synthase levels[29] and impaired transport mechanisms.[30] The addition of FA to the 5-FU regimen has not improved response rates in patients who have developed resistance to 5-FU or in those who are intrinsically resistant.[28,31]

Combination Therapy for Liver Metastases

Most strategies that attempt to increase response rates in patients with unresectable liver metastases from colorectal cancer involve the addition of an adjuvant to the first-line combination of 5-FU/FA. The modulators that have been tested to effect this goal include interferon-α and various chemotherapeutic agents. The addition of interferon-α has resulted in modest responses[32] or no benefit.[33] The addition of chemotherapeutic agents has met with mixed success. Biochemical modulation of 5-FU with methotrexate has not provided significant improvement after failure of 5-FU/FA alone.[34,35] These regimens have shown only minimal effectiveness for the management of patients with unresectable liver metastases beyond that of palliative care.

Oxaliplatin, a 1,2-diaminocyclohexane platinum derivative that is well tolerated, has shown significant response rates in patients with metastatic colorectal cancer resistant to 5-FU.[36-39] With a FOLFOX-2 biweekly regimen (oxaliplatin 100 mg/m^2 on day 1 plus FA 500 mg/m^2 as a 2-hour infusion followed by 5-FU, 1.5 to 2 g/m^2 as a 24-hour infusion on days 1 and 2), the response rate of liver metastases (44% objective response) was similar to that of the primary tumor (46%).[36]

Chronomodulated Therapy

Because various preclinical and clinical studies with cisplatin have shown that the effectiveness of the administered dose and its toxicity vary with the time of day at which the drug is administered,[40-42] chronomodulated schemes of delivery have been devised. In a randomized multicenter trial of 92 patients with metastatic colorectal cancer,[43] a sequentially chronomodulated scheme (Fig 1) of oxaliplatin (25 mg/m^2/d), delivered from 10:00 AM to 10:00 PM and peaking at 4:00 PM and FA (300 mg/m^2/d) plus 5-FU (600 mg/m^2/d) delivered from 10:00 PM to 10:00 AM and peaking at 4:00 AM was compared with a continuous-infusion scheme using the same drug levels. The 5-day

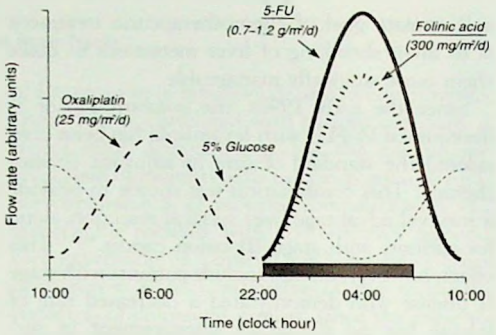

Fig 1. Sequential chronomodulated scheme of oxaliplatin and 5-FU/FA delivery. (Adapted and reprinted with permission.[45])

treatments were repeated every 21 days. Response rates were superior in patients in the chronomodulated group. In addition, after a median number of nine courses of therapy, more patients in the chronomodulated group became eligible for surgery to have metastases removed and more patients achieved a complete response after surgery than those in the continuous-infusion group (Table 1). These results were confirmed in a recent, larger trial of 186 patients[44] that also investigated the resectability of previously unresectable metastatic colorectal cancer, irrespective of the site of metastatic involvement, but including liver, lung, and lymph node metastases. It was clearly demonstrated that a chronomodulated oxaliplatin–5-FU/FA regimen not only provides postchemotherapy response rates superior to those obtained with a continuous-infusion regimen, but also causes sufficient metastasis reduction to allow surgery and to increase the complete response rate after the procedure. Compared with continuous infusion, the chronomodulated regimen also reduced the incidence of 5-FU–induced grade 3/4 mucositis from 76% to 14% (P = .0001) and oxaliplatin-related grade 2 peripheral sensitive neuropathy from 31% to 16% (P = .01).[44]

In a subsequent phase II study of patients treated with a similar chronomodulated regimen in which 5-FU was infused at a rate of 700 mg/m^2/d (instead of 600 mg/m^2/d), a relationship between objective response and the cumulative dose of 5-FU administered was noted. This suggested that the chronomodulated delivery scheme, permitting the delivery of higher doses of 5-FU with less toxicity,

Table 1. Comparison of Response Rates, Ability to Resect Previously Unresectable Tumors, and Postsurgery Response Rates in Patients Treated With a Chronomodulated Versus a Continuous Infusion of an Oxaliplatin/5-Fluorouracil/Folinic Acid Regimen in Two Consecutive, Randomized, Multicenter Trials

	Chronomodulated Regimen (%)		Continuous Infusion Regimen (%)	
	Lévi et al[43]	Lévi et al[44]	Lévi et al[43]	Lévi et al[44]
No. of patients	45	93	47	93
Complete response	3 (7)	5 (5)	2 (4)	3 (3)
Partial response	21 (47)	42 (45)	13 (28)	24 (26)
Eligible for surgery after chemotherapy	17 (38)	23 (25)	11 (23)	17 (18)
Complete response after surgery	12 (27)	20 (22)	5 (11)	13 (14)

would produce higher response rates. The effect of chemotherapy on the resectability of previously unresectable liver metastases was also assessed.[45] The treatment allowed the complete resection of liver metastases in 38% of chemotherapy-naive patients and in 22% of those who had undergone previous 5-FU chemotherapy in a bolus or continuous mode of administration without oxaliplatin (Table 2). This trial showed that previously unresectable liver metastases from colorectal cancer could be resected following chemotherapy with a chronomodulated oxaliplatin–5-FU/FA regimen, even in patients who have become resistant to 5-FU or who are refractory to this agent. However, achieving postchemotherapy resectability was somewhat more likely in chemotherapy-naive patients.

The ability to achieve resectability in patients with previously unresectable liver metastases from colorectal cancer was examined in detail in a recent study reflecting a cumulative single-institution experience and using chronomodulated therapy with oxaliplatin and 5-FU/FA.[46] Of 434 patients with metastatic colorectal cancer seen at Paul Brousse Hospital, 330 had unresectable liver metastases at the time of admission. This inoperable group was treated with a chronomodulated regimen of oxaliplatin (25 mg/m^2/d), 5-FU (700 to 1,200 mg/m^2/d), and FA (300 mg/m^2/d) according to the scheme shown in Fig 1. Each course of chemotherapy lasted 4 to 5 days and was repeated every 3 to 4 weeks. The patients were periodically reassessed with abdominal computed tomography scans. Resection of previously unresectable liver metastases became possible in 53 patients (16%) following chemotherapy. Resections were performed when the tumor size (after repeated computed tomography scans) and the serum carcinoembryonic antigen levels (after repeated measurements) had reached a plateau. The average time required for chemotherapy to reduce the size of the tumor to allow resection was approximately 8 to 9 months. Surgery was curative in 75% of the cases in which it was felt that resection had a good chance of success. The tumor characteristics, cause of unresectability before chemotherapy, duration of chemotherapy, and response rates are shown in Table 3. Initially, hepatic recurrence was observed in 34 patients (64%) during a mean follow-up of 42 months. Hepatic recurrence necessitated a second resection in 15 of these 34 patients (44%), and a third hepatectomy was required in three patients with multinodular metastases. In addition, extrahepatic recurrences that included intra-abdominal and pulmonary metastases developed in 25 patients (47%). Pulmonary metastases occurred mainly in the group of patients who had prior unresectable multinodular liver metastases. Six of the 14 patients with pulmonary metastases were successfully resected.

Table 2. Response Rates and Postchemotherapy Resectability of Previously Unresectable Liver Metastases in Previously Treated and Chemotherapy-Naive Patients Treated With a Chronomodulated Regimen of Oxaliplatin/5-Fluorouracil/Folinic Acid

	Previously Treated Patients, n = 37 (%)	Chemotherapy-Naive Patients, n = 13 (%)
Complete response	1 (3)	2 (15)
Partial response	14 (38)	7 (54)
Complete resection	8 (22)	5 (38)

Table 3. Prechemotherapy Tumor Characteristics, Chemotherapy Regimen, and Response to Postchemotherapy Surgical Resection in Patients With Previously Unresectable Liver Metastases

	Cause of Unresectability				
	Large	Ill-Located	Multinodular	Extrahepatic	Total
No. of patients*	8	8	24	13	53
Largest tumor diameter (mm)*	83 (40-135)	55 (35-80)	37 (14-70)	42 (15-74)	
No. of metastases*	2.5 (1-5)	1.6 (1-3)	6.2 (3-11)	3.2 (1-8)	
Bilateral disease (%)	3 (37)	1 (12)	18 (75)	7 (54)	
Segments involved*	3.8 (2-6)	2.3 (1-3)	4.5 (2-8)	2.8 (1-5)	
CEA levels (ng/mL)*	376 (7-1720)	213 (3-1560)	50 (1-212)	116 (4-350)	
Chemotherapy courses*	7.5 (4-11)	10 (3-19)	9.9 (4-29)	11 (7-18)	
Duration of chemotherapy*	6.5 (2-10)	7.7 (2-17)	7.9 (3-29)	9.5 (6-14)	
Curative resections (%)	7 (88)	8 (100)	19 (79)	12 (92)	46 (75)
Mean follow-up (mo)*	51 (30-84)	35.9 (26-53)	44 (25-85)	38.4 (25-69)	42.1 (25-85)
Hepatic recurrence (outcome)	4	4	13	6	27
Disease free (%)	4 (50)	3 (37)	9 (37)	3 (23)	19 (36)

Abbreviation: CEA, carcinoembryonic antigen.

* Mean value (range).

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After 42 months of follow-up, 26 patients were alive (49%), 19 of whom were disease free (36%) (Table 3). Overall patient survival was 54% and 40% at 3 and 5 years, respectively (Fig 2). The 5-year survival rate according to cause of unresectability of tumor before treatment was 75% for ill-located tumors, 62% for large tumors, 37% for multinodular tumors, and 14% for associated extrahepatic tumors. As expected, focused liver metastases (ill-located or large) were more likely to be amenable to treatment than multiple-site tumors.

These studies demonstrated that a chronomodulated regimen of chemotherapy consisting of oxaliplatin and 5-FU plus FA can be aggressively combined with surgery to ameliorate the prognosis of patients with metastatic colorectal cancer and can significantly prolong survival for some who were originally classified as palliative care candidates.

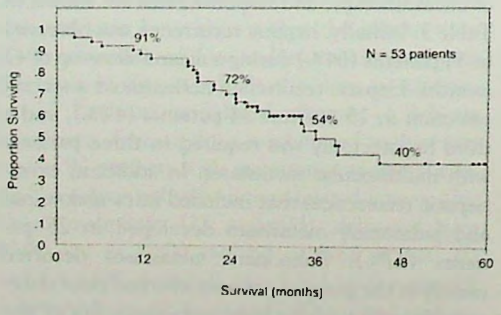

Fig 2. Cumulative survival after liver resection following systemic chronomodulated chemotherapy for all unresectable liver metastases. (Adapted and reprinted with permission.[46])

CONCLUSION

Colorectal cancer preferentially metastasizes to the liver, the lung, or both. Hepatic metastases are the most frequent, and the proportion of patients who can achieve a cure from hepatic resection is estimated to be ≤10%.[47,48] This outcome results from the high proportion of patients with metastatic disease who present with unresectable liver metastases. For these patients, the combination chemotherapy of 5-FU and FA has long been the main palliative option available. However, the outcome is uniformly poor, with tumor response rates rarely exceeding 20% and survival rates ranging from 3 to 6 months in patients with bilobal involvement. A major reason for the mediocre outcome is that patients often become resistant to 5-FU or are intrinsically nonresponsive. Although various combinations of 5-FU/FA with other agents have been tested to try to achieve a better response, these attempts have met with little success because of either minimal improvement or enhanced toxicity.

Recently, the combination of 5-FU/FA with oxaliplatin has provided improved response rates with conventional-administration drug schemes. These rates have been further enhanced with concomitant decreased toxicity by using a chronomodulated regimen. These studies have shown that previously unresectable liver metastases from colorectal carcinoma can be reduced to the point of resectability, resulting in significant response rates and prolonged survival. Among previously noncurable patients, 16% can eventually become resectable, with approximately 40% of these surviving at least 5 years.

These results suggest that for patients with no extrahepatic involvement, improved resection technique (including cryotherapy and embolization for difficult-to-manage liver metastases) and an effective chemotherapeutic regimen rigorously administered to make unmanageable metastases amenable to resection will help change previously bleak prognoses. Even patients with metastatic disease can look forward to prolonged survival.

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Oxaliplatin for the Treatment of Advanced Colorectal Cancer: Future Directions

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The introduction of oxaliplatin into the colorectal cancer setting represents a significant advancement in the treatment of the disease. Synergistic effects with traditional therapy 5-fluorouracil/folinic acid have increased response rates significantly, improved time-sensitive response parameters, and facilitated the removal of previously unresectable hepatic metastases, thus changing the natural history of the disease. Ongoing and planned trials are identifying various issues that need to be addressed to fully realize the potential of oxaliplatin. These include optimization of dosing and schedule of administration, determination of the most effective oxaliplatin–5-fluorouracil/folinic acid combination, definition of the role of new thymidylate synthase inhibitors with respect to oxaliplatin therapy, and identification of the most effective combinations of oxaliplatin with the new anticancer agents that have been recently introduced. Providing the answers to these questions will contribute to changing the attitude of the clinical oncologist regarding what strategy to adopt in treating colorectal cancer in the coming years.

FOR OVER 40 YEARS, the mainstay of adjuvant chemotherapy for the treatment of advanced colorectal cancer has been 5-fluorouracil (5-FU), which, when administered as a single agent, rarely achieves response rates higher than 15%.[1-3] In addition, there is still no consensus as to the most effective dosage, schedule, or route of administration of 5-FU. Because the biochemical modulator folinic acid (FA) enhances the antitumor activity of 5-FU, these agents are often combined to improve objective response rates.[4,5] An increase in response rates, however, does not usually translate into an improvement in patient survival.[5,6] Whereas continuous protracted infusion results in statistically significant improvement in time to progression and patient survival over bolus administration,[7] the statistically significant survival advantage of approximately 1 month has limited clinical relevance, and therefore bolus administration remains the preferred modality. Consequently, clinical research efforts have concentrated on the development of other antitumor agents for use alone or in combination with 5-FU.

Our current understanding of colorectal carcinogenesis and tumor progression at the molecular level, including the role of p53 in cell cycle progression and apoptosis,[8,9] the role of deficient mismatch repair in nonpolyposis familial colorectal cancer,[10,11] and the role of thymidylate synthase activity in resistance to 5-FU therapy,[12] has suggested new therapeutic strategies and provided insight into the treatment-dependent natural history and prospective therapeutic outcome of this disease. New agents currently under development for the treatment of colorectal cancer include the third-generation platinum derivative oxaliplatin; the thymidylate synthase inhibitors raltitrexed, UFT (uracil and tegafur), and capecitabine; the antimetabolite gemcitabine; and the topoisomerase I inhibitor irinotecan (CPT-11).[2,13-20] This recently acquired knowledge will require us to redefine the management of colorectal cancer and carefully determine optimal combinations, schedules, and sequence of administration of the newly available agents. Raltitrexed, CPT-11, and oxaliplatin have been the object of the most intensive and advanced development, with the oxaliplatin–5-FU/FA combination yielding the highest efficacy levels against advanced colorectal cancer in both pretreated and chemotherapy-naive patients.

The recent introduction of oxaliplatin in combination with 5-FU/FA has consistently increased objective response rates to over 40%, even in 5-FU–refractory patients.[2,21] The administration of these agents in a chronomodulated schedule appears to be less toxic than continuous infusion and provides even higher response rates.[22] The effectiveness of this combination has facilitated the surgical removal of distant metastases (particularly hepatic metastases) in patients whose tumors were previously unresectable.[23] The favorable safety profile of oxaliplatin (see Extra et al elsewhere in this

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supplement [pp 13–22]) has allowed the treatment of thousands of patients, with limited gastrointestinal and hematologic toxicities and no life-threatening toxicity or morbidity other than sporadic, acute pharyngolaryngeal dysesthesia or cumulative, self-limiting, and mostly reversible neurosensory toxicity.[24]

The physicians most experienced in using oxaliplatin have grasped the therapeutic possibilities of this new agent. The uniqueness of its mechanism of action and its additivity and/or synergy with many other agents, together with the simultaneous availability of CPT-11,[14,18,25,26] the ongoing development of new thymidylate synthase inhibitors, and the increasing prevalence of adjuvant treatment in patients with colorectal cancer, provide a major opportunity to redefine and optimize the currently available therapeutic decision algorithms for this disease.

Since the spectacular results obtained in 5-FU–refractory disease with the oxaliplatin–5-FU/FA combination have become known, a large number of trials have been planned and carried out to optimize the parameters of oxaliplatin administration and to define its place in the colorectal cancer setting. However, there is still much to be learned regarding the most effective method of administration of this antitumor agent, both as a single agent and in combination therapy. Currently, more than a dozen planned and ongoing clinical trials with oxaliplatin in patients with advanced colorectal cancer are attempting to answer the outstanding questions, some of which are addressed below.

WHAT IS THE OPTIMAL DOSE AND SCHEDULE OF OXALIPLATIN?

The currently recommended dose of oxaliplatin is 130 mg/m^2 administered intravenously (IV) over 2 to 6 hours every 3 weeks. However, other schedules have not been attempted for single-agent administration of oxaliplatin. Both de Gramont and Lévi have used oxaliplatin in combination with 5-FU/FA at biweekly doses of 85 to 100 mg/m^2 either as a 2-hour infusion or over 4 to 5 days as a chronomodulated infusion (see these reports elsewhere in this supplement [pp 32–39]). The dose intensity (35 to 40 mg/m^2/wk) of such schedules is similar to that of the 130 mg/m^2 every 3 weeks schedule, and to date, there appear to be no apparent differences in overt toxicity or in the rate, severity, and reversibility of cumulative dose-dependent neurotoxicity. Chronomodulated administration, however, appears to be less toxic.[21] As in most phase I studies, pharmacokinetics considerations were not addressed, particularly with respect to the ability of such schedules to maintain the initial dose of oxaliplatin over five or six cycles of therapy. The formal comparison of the incidence and severity of toxicity resulting from a biweekly oxaliplatin schedule, designed to increase the overall therapeutic index, versus a triweekly schedule has not yet been published. Three ongoing, multicenter, randomized phase II trials do have both biweekly and triweekly regimens in their design (Table 1).

The dose-limiting neurotoxicity of oxaliplatin appears as the crucial end point in the determination of optimal dosing schedules. The specific neurotoxicity scale devised by Caussanel et al[27] was based on an open randomized phase I design that allowed for observer bias in the assessment of the subjective acute neurosensory toxicity. Since then, it has undergone several minor changes in consecutive studies, making impossible a formal comparison of the different doses and schedules of administration. Additional variables affecting the severity of acute dysesthesia include length of infusion (probably the length of time it takes free plasma platinum to achieve ≥75% protein binding), exposure to cold, and the education of both prescriber and patient.

The length of infusion may also be responsible for the differential emesis and antiemetic needs observed with the short infusion (2 to 6 hours IV) versus 4- to 5-day chronomodulated administration, which clearly lead to different maximum platinum concentrations, although severe oxaliplatin-induced emesis is well controlled with standard doses of modern anti–5-HT$_3$ antiemetics.

Because of these factors, the maximal tolerated dose and the recommended dose of oxaliplatin need to be redefined in terms of appropriate cycle frequency and various lengths for short infusions, particularly when the total number of courses planned is fewer than six, as in the adjuvant and neoadjuvant settings. Disease-specific phase I/II trials in head and neck cancer and malignant melanoma have been proposed to redefine the maximal tolerated dose and recommended dose of the triweekly schedule, with an infusion time of 4 to 6 hours. A pharmacokinetics assessment of free platinum and protein-binding correlates is necessary to clarify these issues in the appropriate clinical trials.

Table 1. Protocol of Four-arm Randomized Multicenter Phase II Trials of Oxaliplatin Currently in Progress in the United States and Europe

	Modalities			
Trial	Fluoropyrimidine	Administration	Oxaliplatin	Administration
Advanced colorectal cancer: first line				
US trial, 160 patients	LV5-FU2	CIV 48 hr	85 mg/m^2	Biweekly
	5-FU/FA	Weekly bolus	85 mg/m^2	Biweekly
	5-FU/FA	Chronomodulated	130 mg/m^2	Triweekly
	5-FU	CIV	130 mg/m^2	Triweekly
Advanced colorectal cancer: second line				
US trial, 200 patients	5-FU	CIV	130 mg/m^2	Triweekly
	5-FU (high-dose)/FA	CIV 24 hr, weekly	85 mg/m^2	Biweekly
	5-FU/FA	IV bolus (5 d/mo)	130 mg/m^2	Triweekly
	5-FU/FA	IV bolus weekly	85 mg/m^2	Biweekly
European trial, 200 patients	5-FU	CIV	130 mg/m^2	Triweekly
	5-FU (high-dose)/FA	CIV 24 hr, weekly	85 mg/m^2	Biweekly
	5-FU/FA	CIV	85 mg/m^2	Biweekly
	5-FU/FA	IV bolus (5 d/mo)	130 mg/m^2	Triweekly

Abbreviations: LV5-FU2, leucovorin 200 mg/m^2/d, 2-hr infusion, then 5-FU bolus 400 mg/m^2/d and 5-FU 600 mg/m^2/d, continuous intravenous (CIV) 22-hr, all repeated for 2 consecutive days.

The issues of tolerance, toxicity, and cumulative toxicities with the every 2 weeks versus every 3 weeks schedule are being formally addressed in three randomized, multicenter, four-arm phase II trials in the United States (as first-line therapy) and in Europe (as second-line therapy). Two of these trials are being conducted in pretreated patients (one in the United States, one in Europe), and one trial is being conducted in previously untreated patients (in the United States) (Table 1). Since the planned dose intensity is the same in all arms, the results should settle the issue of cycle frequency. The weekly administration of oxaliplatin in combination with 8-hour weekly 5-FU/FA IV will be explored in a trial by Gamelin and coworkers (personal communication, February 1998).

WHAT IS THE MOST EFFECTIVE 5-FLUOROURACIL/FOLINIC ACID COMBINATION WITH OXALIPLATIN?

Over 40 years of clinical research on 5-FU schedules has shown that FA or methotrexate modulation increases response with an adequate safety profile, but has little effect on time-related efficacy parameters, and that infusional 5-FU delivery has pharmacodynamic effects and a toxicity profile unlike those observed with bolus administration.[28,29] Infusional delivery appears to be active in 5-FU bolus failures and prolongs survival with statistical significance, but with borderline clinical relevance when the quality of life of the patient and infrastructural logistic constraints are considered.[7]

It is unlikely that oxaliplatin will help clarify the controversy regarding 5-FU delivery. However, it should be noted that most, if not all, available data on oxaliplatin and 5-FU have been obtained with infusional high-dose 5-FU/FA schedules, with little dependence on the dose or stereospecificity of the FA administered.[30] To date, however, high-dose infusional 5-FU/FA schedules have given the best response rates or time-related parameters in advanced colorectal cancer.[28]

The three randomized, multicenter, four-arm phase II trials are addressing this issue head on, since the contribution of the 5-FU dosing schedule and administration modality should be analyzed in terms of progression-free and overall survival rates rather than response rate, an admittedly poor efficacy surrogate in advanced colorectal cancer.[31]

The efficacy of biweekly administration of chronomodulated 5-FU/FA for 4 days will be compared with the 48-hour FOLFOX delivery schedule developed by de Gramont (see Bleiberg and de Gramont in this supplement, pp 32-39) with oxaliplatin given over a 2-hour period, in a random-

ized phase III trial conducted by the recently created Chronotherapy Group of the European Organization for Research on the Treatment of Cancer. Smaller studies with chronomodulated oxaliplatin–5-FU/FA delivered every 2 weeks have shown a higher response rate and a shorter time to response than the previous 5-day schedule every 3 weeks.[21,32] The resolution of these issues is important, because it has been suggested that this biweekly mode of administration has improved the chances of removing previously unresectable hepatic metastases.

Another trial conducted by Bertheault-Cvitkovic will attempt to improve on the 5-FU/FA 48-hour delivery schedule of de Gramont, using chronomodulated delivery of 5-FU/FA, with oxaliplatin given over 6 hours (personal communication, July 1997).

In a trial aimed at further intensifying the frequency of delivery, Gamelin and coworkers will formally study a weekly 8-hour 5-FU/FA delivery schedule in a phase I/II study, with the simultaneous weekly administration of oxaliplatin.

The FOLFOX-2 schedule, previously reported by de Gramont et al (see Bleiberg and de Gramont in this supplement, pp 32-39) as a biweekly treatment, is being administered every 3 weeks by Rougier et al, and the results of this study will be reported shortly (Rougier, personal communication, January 1998). Interesting variations in 5-FU delivery are currently undergoing evaluation in China and South America. Additionally, a 70-patient phase II trial in Argentina is comparing biweekly administration of oxaliplatin (85 mg/m^2) with oxaliplatin (biweekly, same dose) plus 5-FU/FA, day 1 to 5 every 4 weeks.

Currently, there are no published data on the use of oxaliplatin with protracted 5-FU continuous IV infusion. However, one of the ongoing four-arm phase II trials includes 5-FU continuous IV administration (Table 1). An ongoing French multicenter, randomized trial of patients with advanced colorectal cancer refractory to 5-FU is also addressing this issue. In this trial, patients in one arm are treated with irinotecan, and patients in the other two arms are treated with protracted 5-FU continuous IV infusion; patients in one of the latter arms also receive oxaliplatin (Table 2; Adenis, personal communication, July 1997). Pharmacokinetics issues concerning the long-term administration of 5-FU continuous IV infusion with oxaliplatin are being addressed in another phase I/II trial by Cunningham and coworkers (personal communication, July 1997).

Table 2. Multicenter Randomized Phase III Trial of 212 Patients With Advanced Colorectal Cancer Refractory to 5-FU

RANDOMIZE	Arm 1: 106 patients	5-FU 250 mg/m^2 CIV + oxaliplatin 130 mg/m^2 triweekly
	Arm 2: 53 patients	5-FU 300 mg/m^2 CIV d 1-49, rest 2 wk
	Arm 3: 53 patients	Irinotecan 350 mg/m^2 triweekly

NOTE. This three-arm trial compares 5-FU alone and 5-FU plus oxaliplatin modalities with triweekly irinotecan. Response rates, toxicity of each regimen, and quality of life according to the QLQC-38 protocol will be assessed.

Abbreviation: CIV, continuous intravenous.

WHAT IS THE ROLE OF THE NEW THYMIDYLATE SYNTHASE INHIBITORS?

The new thymidylate synthase inhibitors (raltitrexed, capecitabine, UFT) differ from 5-FU in their ease of administration, metabolism, and increased tissue selectivity; however, their efficacy and toxicity profiles are essentially the same as those of 5-FU. Not surprisingly, these agents are being or will be tested in combination with oxaliplatin. Both capecitabine and UFT are being or will be orally administered agents with superior selectivity and metabolic profiles. Although they have shown convincing efficacy and safety profiles in hundreds of patients, their therapeutic advantage as single agents in patients with advanced colorectal cancer will be limited by the same barriers that 5-FU modulators have confronted.

A recent phase I trial of raltitrexed and oxaliplatin has been completed by J. P. Armand (personal communication, November 1997) using the full recommended doses for both agents (3 mg/m^2 and 130 mg/m^2, respectively) administered every 3 weeks. A phase II trial of this combination will be conducted in previously untreated patients with advanced colorectal cancer by investigators from the French Federation of Anticancer Centers.

WHAT COMBINATIONS OF OXALIPLATIN WITH OTHER AGENTS ARE ACTIVE IN COLORECTAL CANCER?

The topoisomerase I inhibitor irinotecan, already registered in most countries, has shown activity both in chemotherapy-naive patients and in 5-FU–pretreated patients. On the basis of the synergistic activity observed in vitro with oxaliplatin and SN-38, the active metabolite of irinotecan,[33] a phase I study using oxaliplatin and CPT-11 was conducted and reported recommended doses of 200 mg/m^2 for irinotecan and 85 mg/m^2 for oxaliplatin.[34] In this trial of 17 patients with advanced colorectal cancer, 13 of whom were resistant to 5-FU, seven had an objective response. A similar phase I study conducted by Marty and coworkers is near completion, and a comparable study with biweekly administration is ongoing.[35] Another biweekly study will be initiated in the United States by Rothenberg (personal communication, November 1997), and a weekly administration schedule will be explored by N. Kemeny at Memorial Sloan-Kettering Cancer Center (personal communication).

Oxaliplatin synergy with gemcitabine in vitro has been recently described.[36] A phase I/II study is planned for patients with advanced colorectal cancer, as well as for other indications. Tirapazamine is a new bioreductive agent with clear activity with a variety of cytotoxic agents. Because the combination of 5-FU, cisplatin, and mitomycin (another bioreductive agent) has shown activity in colon cancer xenografts,[37] it would be logical to test the combination of 5-FU, oxaliplatin, and tirapazamine.

Alternative treatment strategies with oxaliplatin are being addressed in specific trials of radiochemotherapy for rectal cancer and intra-arterial infusion in patients with hepatic metastases.

OXALIPLATIN IN THE THERAPEUTIC STRATEGY AGAINST COLORECTAL CANCER: CURRENT ASSESSMENT AND FUTURE PROSPECTS

After a very long period in which the only therapeutic approach to colorectal cancer was the optimization of fluoropyrimidine-based therapy, new therapeutic possibilities make the next decade in gastrointestinal oncology an exciting arena. It is obvious that the introduction of oxaliplatin in the treatment of colorectal cancer has changed the natural history of the disease, not only because the addition of oxaliplatin to the traditional 5-FU/FA regimen has increased response rates consistently to the 35% to 55% range, with longer time to progression and survival than previously reported, but also because patients who ceased to respond to traditional fluoropyrimidine-based therapy show renewed response when oxaliplatin is added. At present, first-line treatment of advanced disease is an indication that has recently been accepted by French regulatory authorities. It is expected that the last completed phase III study will confirm the excellent activity noted in previous phase II and phase III trials. The adjuvant setting is the obvious next step to consider, since beneficial effects can be expected in a clinical setting in which there is less tumor burden. Consequently, studies in both Dukes' stage C patients and very high-risk patients ($\geq$4 nodes, perforation, focal peritoneal seeding) are being planned and initiated in 1998.

The experience with postchemotherapy resection of previously unresectable hepatic metastases has been particularly rewarding. Because of this development in patients with metastatic colorectal cancer, the attitude of the physician has changed concerning cases previously deemed untreatable, and patients with hepatic metastases can look forward to prolonged survival and a decreased incidence of relapse after hepatic resection. It is evident that familiarity with the combination regimen and the availability of experienced and motivated surgical teams working closely with the medical oncologists are the main determinants of the growth of such a therapeutic strategy. In this respect, a major change in therapeutic strategy, taking into account the possibility of eventual resection before starting chemotherapy, is already being considered for patients in many French and other European centers. Aggressive therapy with new combinations presently under development may also provide the means to treat patients with extrahepatic metastases.

That such initiatives are welcome and need to be encouraged is clear. Clinical trials may allow us to define the most beneficial modalities for the greatest proportion of patients. Of importance in this regard is the exciting and rapidly evolving growth of clinicobiochemical studies correlating insights gained from molecular biology with prognostic and natural history parameters, some of

Table 3. Potential Anticancer Agent Combinations for Future Colorectal Cancer Therapy

Indication	Phase	Drugs
Ongoing studies		
Colon cancer, pretreated	III	LV5-FU2 alone or with oxaliplatin 85 mg/m^2
Colon cancer, pretreated	II	Oxaliplatin 85 mg/m^2 + CPT-11 200 mg/m^2 every 3 wk v oxaliplatin 85 mg/m^2 + CPT-11 200 mg/m^2 every 3 wk alternated with CPT-11/LV5-FU2
GI malignancies, pretreated	II	Oxaliplatin/CPT-11 every 2 wk
GI tumors	I	Oxaliplatin/raltitrexed
Planned studies	III	
Colon cancer, adjuvant		Oxaliplatin–5-FU/FA v 5-FU/FA
Colon cancer, pretreated	III	Oxaliplatin–5-FU/FA chronomodulated v oxaliplatin–5-FU/FA (LV5-FU2)
Colon cancer, untreated	II	Oxaliplatin/CPT-11 every 2 wk
Gastric cancer, untreated	II	Oxaliplatin-5-FU/FA (LV5-FU2) every 3 wk

Abbreviations: LV5-FU2, leucovorin 200 mg/m^2/d, 2-hr infusion, then 5-FU bolus 400 mg/m^2/d and 5-FU 600 mg/m^2/d, continuous intravenous (CIV) 22-hr, all repeated for 2 consecutive days; GI, gastrointestinal.

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which are treatment dependent (for example, thymidylate synthase). Mismatch repair deficiency has not been studied as a treatment-dependent prognostic parameter in colorectal cancer, but studies are planned.

Tactical issues are of more immediate concern vis-à-vis the positioning of oxaliplatin, CPT-11, and the combination of these with 5-FU/FA. Many such studies are being planned or are ongoing. The triple combination of the simultaneous administration of a thymidylate synthase inhibitor (5-FU/FA or raltitrexed), oxaliplatin, and CPT-11 is in an early exploratory phase. The administration of all three drugs is being studied in a variety of large multicenter trials, some of which are randomized phase II or III studies, comparing different combinations and sequences of administration (Table 3).

The exciting and innovative trials that are already accruing patients or are close to startup are only a small indication of the renewed interest in the clinical research focused on colorectal cancer. The past decade has seen trends for clinical studies that seek to establish the benefit to risk ratio of various treatments, with a baseline judgment that not much improvement in time-related therapeutic outcome was to be expected. The results reported with oxaliplatin have changed this attitude and, it is hoped, will also change therapeutic outcomes.

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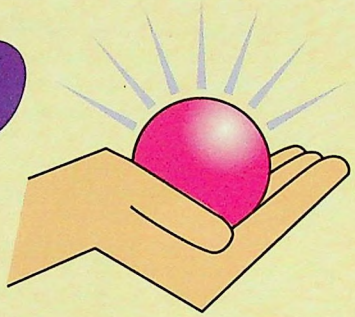

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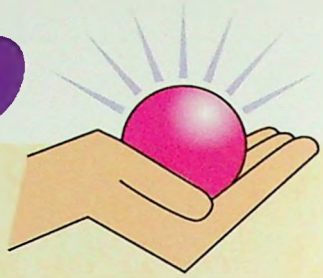

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New Treatment Strategies for Malignant Gliomas

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Key Words. *Glioma · Chemotherapy · Gene therapy · Angiogenesis · Clinical trials · Antisense · Cytokine · Immunotherapy*

ABSTRACT

Although survival in patients with malignant gliomas remains limited, there is renewed optimism with the emergence of novel treatment strategies. Cytotoxic agents such as temozolomide and CPT-11 have shown promising clinical activity. Biological treatments for brain tumors, including antisense oligonucleotides, gene therapy, and angiogenesis inhibitors, are also being evaluated in clinical trials. Delivery strategies have been developed to overcome challenges presented by the blood-brain barrier. These noteworthy treatments, alone or in combination, may ultimately prolong survival and enhance quality of life in this group of patients. *The Oncologist 1999;4:209-224*

INTRODUCTION

While primary malignant brain tumors account for only 2% of all adult cancers, these neoplasms cause a disproportionate burden of cancer-related disability and death. The five-year survival rates for brain tumors are the third lowest among all types of cancer (pancreas and lung are first and second, respectively). Malignant gliomas (glioblastoma multiforme [GBM] and anaplastic astrocytoma [AA]) comprise the most common types of primary central nervous system (CNS) tumors and have a combined incidence of 5-8/100,000 population. The median survival of patients with malignant gliomas treated conservatively is 14 weeks; by surgical resection alone, 20 weeks; by surgery and radiation, 36 weeks; and by the addition of chemotherapy, 40-50 weeks [1-4]. Although survival for GBM has not changed significantly over the past three decades, the emergence of novel treatment strategies for these tumors has led to heightened interest and optimism among oncologists.

CLINICAL TRIAL DESIGN

The history of clinical trials for brain tumors is replete with examples of poor study design and ambiguous results (Table 1) [5, 6]. One of the challenges for testing new agents in this disease is the fact that brain tumors are uncommon, one-tenth as frequent as breast or lung cancer. Therefore, an unlimited number of large, prospective, randomized, controlled studies is not possible. As a result, there is reliance on nonrandomized studies as the principal design for the identification of potentially active therapies that should be studied in more definitive, randomized trials.

The decision to proceed with larger, more expensive and time-consuming randomized studies should be based on carefully designed and conducted phase I trials to define the maximum tolerated dose and toxicity, and on phase II trials to define efficacy. Because enzyme-inducing (CYP450) antiepileptic drugs (AED) enhance the metabolism and inactivation of certain chemotherapies, phase I trials of new agents that undergo hepatic metabolism should be conducted in patients with brain tumors stratified into those on CYP450 inducers and those not on such agents with independent dose escalations in each arm [7, 8]. This will avoid the possibility of underdosing patients. Despite careful phase II study design and execution, the possibility of selection bias remains, especially if the outcome is progression-free or overall survival. Objective responses on neuroimaging are more likely to indicate activity of a drug, whereas progression-free survival and overall survival may simply reflect patient selection.

To address these challenges, one major brain tumor collaborative group has adopted a paradigm that includes a

Table 1. Historical limitations of brain tumor clinical trials

- ▲ Divergent study entry criteria
- ▲ Inadequate statistical power
- ▲ Use of different outcome measures (tumor response, tumor control, clinical parameters)
- ▲ Inadequate control for known prognostic factors (age, Karnofsky Performance Score, histology)
- ▲ Inadequate control for co-interventions (steroids, treatment at recurrence)

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Table 2. Response criteria for phase II studies of supratentorial malignant glioma

Response	Enhancing tumor area	Neurological status	Steroids
Complete response	≥ 95% decrease	Improved or stable	Off
Partial response	50%-94% decrease	Improved or stable	Stable or decreased dose
Progressive disease	≥ 25% increase	Worsened	Stable or increased dose
Stable disease	All other situations	All other situations	All other situations

combined phase I/II design with dose escalation in two independent arms (CYP450 inducers and non-CYP450 inducers); chemotherapy prior to radiation and primary outcome defined as objective radiographic responses. All patients must have residual, enhancing tumor on postoperative neuroimaging. The radiographic responses are defined along the lines of other oncology trials as outlined in Table 2 [9]. This study design optimizes conditions for defining which agents are active or inactive for newly diagnosed malignant gliomas.

New agents that are cytostatic represent another challenge in the design of clinical trials. Since the predominant effect of these agents is stabilization of tumor size, radiographic response rates are a suboptimal outcome measure. Specifically, direct visualization by computerized tomography (CT) or magnetic resonance imaging (MRI) may be insensitive to capillary number, density, blood flow, and tumor metabolic activity. Despite the limitations of progression-free and overall survival in the context of phase II studies, these endpoints currently serve as the primary outcome measures in the assessment of most cytostatic agents. There is a need to identify biological correlates of activity in these types of studies. Data collected from surrogate studies such as positron emission tomography (PET) scanning, MR spectroscopy, and biopsy with attention to blood vessel morphology and number may be relevant in these regards.

Important issues for phase III trials include stratified randomization for the known prognostic factors (Karnofsky Performance Score [KPS], age, histology) to minimize the chance of unbalanced distribution of these factors in the different arms of the study [10]. Centralized neuropathology review and use of pathologic criteria known to have a high inter-rater correlation (WHO criteria = 94% correlation) are also important [11, 12]. High inter-rater reliability ensures accurate case identification and minimizes misclassification bias.

Analysis of phase III outcomes should begin with examination of predefined primary and secondary outcome measures between the different treatment groups. Further analysis may include multivariate modeling to identify subgroups responsive to therapy. Such subgroup analyses should not serve as the basis for definitive treatment recommendations, but instead should be seen as hypothesis-generating for future studies.

Finally, oncology study outcomes (including brain tumor trials) have traditionally consisted of survival and time to progression of disease. However, patient-derived data based on quality of life (QOL) surveys are becoming more common and desirable. Combination of QOL data with survival data (Q-TWiST analyses [time without symptoms or toxicity]) will be an important means of comparing treatments, especially if survival times are similar [13]. Several QOL measures have been validated in malignant glioma patients (FACT-BR [Functional Assessment of Cancer Therapy-Brain subscale] and the EORTC QLQ-C30 [European Organisation for Research and Treatment in Cancer Quality of Life Questionnaire]) and could be incorporated into a phase III study as an outcome [14, 15]. KPS is not a sufficient measure and does not correlate with QOL measures [14, 16].

Attention to the basic principles of clinical trial design will optimize conditions for identifying active agents in phase II studies and allow such drugs to undergo more definitive testing in randomized controlled trials.

Cytotoxic Agents

Methylating Agents

Temozolomide

Temozolomide is an imidazotetrazinone with activity attributed to the formation of a reactive methyldiazonium cation and methylation of O6-guanine in DNA (Fig. 1). Clinical responses to temozolomide are closely linked to the activity of O6-alkylguanine-DNA alkyltransferase (AGT), a DNA repair protein that removes O6-alkylguanine adducts in DNA [17]. Features of temozolomide that are attractive for use in tumors of the CNS include excellent oral bioavailability and good penetration of the blood-brain barrier (BBB) [18].

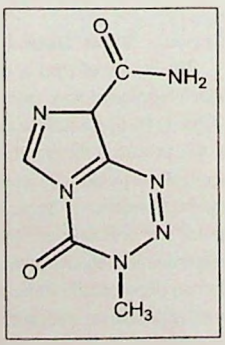

Figure 1. Temozolomide.

The activity of temozolomide is highly dependent on dosing schedule, with multiple administrations being more

Table 3. Summary of clinical trials of temozolomide for malignant gliomas

Author	Path	Study	# Patients	Dose	CR(%)	PR(%)	Remarks
Newlands [19]	GBM AA	Ph-I Rec	3	200 i.v.; 5/28 d +	0 (0)	2 (67)	"Dramatic clinical improvement" reported.
Brock [20]	GBM AA	Ph-I Rec	17	75 p.o.; 7 wks *	0 (0)	7 (41)	An additional 6/17 maintained stable disease. Regimen permitted >2 fold drug exposure/cycle over standard dose.
Newlands [21]	GBM AA	Ph-I/II: N Ph-I/II: Rec	27 48	200 p.o.; 5/28 d +	0 (0) 0 (0)	8 (30) 12 (25)	Survival advantage not demonstrated. Seven patients not assessable by neuroimaging.
Bower [22]	GBM AA	Ph-II: N(5) Rec(98)	103	200 p.o.; 5/28 d +	0 (0)	5 (9)	Only 57 of these patients evaluated with MR/CT of brain. 87% maintained stable disease.
Levin [23]	AA	Ph-II: Rec	161	200 p.o.; 5/28 d +	- (-)	42 (42)	Analysis of first 100 patients only. No breakdown of CR versus PR. 24% of patients maintained stable disease.
Friedman [24]	GBM AA	Ph-II: N	33	200 p.o.; 5/28 d +	3 (9)	14 (43)	No survival data. AGT protein expression may identify patients in whom tumors are resistant to temozolomide.

CR = complete response; PR = partial response; N = neoadjuvant (prior to radiation); Rec = recurrent; GBM = glioblastoma multiforme; AA = anaplastic astrocytoma; i.v. = intravenously; p.o. = orally; d = days; wks = weeks; +150-200 mg/m^2 daily on days 1-5 each 28-day cycle; *75 mg/m^2 daily for seven weeks; AGT = O6-alkylguanine-DNA alkyltransferase.

effective than a single dose. It is administered orally at 200 mg/m^2 daily for five days on a four-week cycle. Peak plasma concentration is achieved within 30-60 min of oral administration and the compound has an elimination half-life of one to two hours. Elimination is largely via renal excretion as intact drug and a carboxylic acid metabolite that has equivalent cytotoxicity. Myelosuppression, which is dose limiting at 1,200 mg/m^2, and nausea and vomiting are the most frequent adverse events [18].

Clinical trials of temozolomide in malignant gliomas are summarized in Table 3 [19-24]. Phase II trials have reported partial responses (PR) in 9%-43% of cases. This activity has been especially promising for AA. New directions for the use of this drug will likely focus on optimizing dosage and delivery to the CNS. For example, temozolomide is compatible with chronic administration as patients have tolerated this drug for up to three years [18]. Additionally, combination with the "pseudosubstrate" O6-BG (O6-benzylguanine) is a promising approach since O6-BG irreversibly inactivates AGT and potentially increases the efficacy of temozolomide treatment [17].

Topoisomerase I Inhibitors

The camptothecin analogs CPT-11, topotecan, and 9-aminocamptothecin (9-AC) exert their cytotoxic effects by inhibiting topoisomerase I. Normally, topoisomerase I tyrosine undergoes a reversible trans-esterification reaction with the 3′ end of the DNA strand. This cleaves the strand long enough to allow passage of a newly synthesized strand through the cut, after which time topoisomerase I normally reseals the cleavage. The cytotoxic effect of camptothecins is exerted during replication by their ability to bind and stabilize this DNA-topoisomerase I complex. An irreversible double-stranded DNA break occurs at the time of collision of the replication fork and cleaved DNA strand (Fig. 2). However, the correlation of cellular topoisomerase I levels to drug sensitivity has been difficult to establish [25].

Topoisomerase I inhibitors studied as potential treatments of gliomas include CPT-11, topotecan, and 9-AC. The in vitro activity of these camptothecins in human colon carcinoma HT-29 cells has been compared with the following cytotoxic potency established: SN-38 (metabolite of CPT-11) > camptothecin > 9-AC > topotecan > CPT-11 [26]. In GB-1 and U-87MG glioma cell lines, SN-38 induced apoptosis and demonstrated significantly stronger antitumor effects than did CPT-11 [27].

CPT-11

CPT-11 undergoes hydrolysis or de-esterification to form the active metabolite SN-38, which is approximately 100-1,000 times as potent as CPT-11 as an inhibitor of topoisomerase I (Fig. 3) [25, 27]. Because SN-38 is 95% bound to plasma proteins compared to only 65% for CPT-11, the precise contribution of SN-38 to the activity of CPT-11 is unclear. SN-38 can be further metabolized to the inactive SN-38 glucuronide (SN-38G) by hepatic UDP-glucuronyltransferase (UDP-GT) [28]. In an animal model, pretreatment with the AED valproic acid resulted in a 99% inhibition of the formation of SN-38G, leading to a 270% increase in the area under the plasma concentration-time

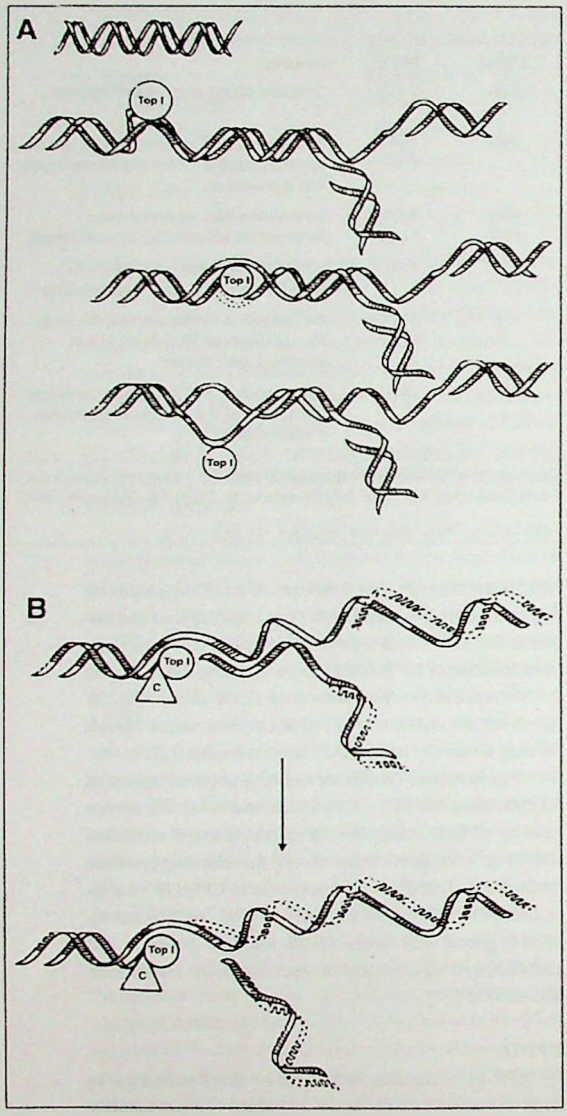

Figure 2. Topoisomerase I. A) The mechanism of topoisomerase I action. (1) Increasing tension and supercoiling of DNA. (2) Topoisomerase I binds to one DNA strand and cuts it (cleavage reaction). (3) The intact strand of DNA passes through the neck, resulting in the relaxation of the torsional strain. (4) Topoisomerase I reseals the broken strand (religation step) and dissociates from the DNA molecule. B) Collision of the replication fork with the camptothecin-stabilized cleavable complex results in an irreversible double-strand break in the DNA. Top I = topoisomerase I; C = camptothecin; solid lines = parent DNA; dotted lines = daughter DNA. Used with permission from [25].

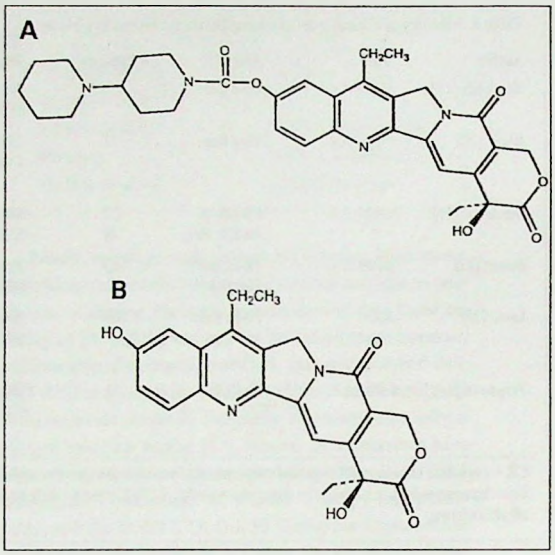

Figure 3. A) CPT-11. B) SN-38.

curve of SN-38 compared with controls [29]. This observation has led to the exclusion of patients requiring valproic acid from most clinical trials of CPT-11.

The initial and terminal half-lives of CPT-11 are approximately 6 h and 10-14 h, respectively. Elimination occurs primarily in the bile and secondarily in the urine. The main toxicities observed with CPT-11 are an acute cholinergic syndrome, delayed onset diarrhea, neutropenia, nausea, vomiting, fatigue, and alopecia. The usual dosing schedule is 125 mg/m^2/week for four weeks followed by a two-week rest [25].

Hare investigated more than 40 drugs in a CNS xenograft model using multiple adult and pediatric glioma cell lines and found CPT-11 to be the most active agent tested [30]. An initial clinical trial of CPT-11 in 60 patients with recurrent malignant glioma resulted in 10/49 (20%) PR in GBM patients and 1/8 (12.5%) PR in AA patients [31]. Ten patients with GBM and three with AA demonstrated stable disease beyond two cycles. Single agent CPT-11 for recurrent malignant gliomas is now the subject of three phase II NCI-sponsored trials.

Topotecan

Topotecan is a topoisomerase I inhibitor that undergoes a reversible pH-dependent hydrolysis of its lactone ring to produce the pharmacologically active form of the drug (Fig. 4). It is then rapidly converted to its inactive carboxylate form at physiologic pH [32, 33]. Topotecan has a

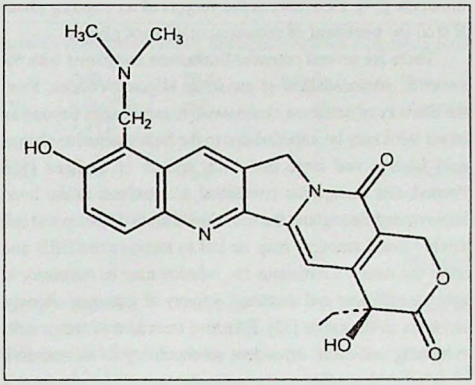

Figure 4. Topotecan.

half-life of two to four h following doses of 0.5 to 1.5 mg/m² administered as a 30-min infusion, and approximately 35% of the drug is protein bound [34]. The antitumor effect of topotecan appears to be greater when the drug is administered over a prolonged period of time compared with an intermittent schedule of drug administration [35]. The drug penetrates the BBB with a cerebrospinal fluid (CSF) to serum ratio of 0.3 [36]. The main toxicities of topotecan are leukopenia and thrombocytopenia; diarrhea and vomiting are less than with CPT-11. Elimination is primarily renal and patients with creatinine clearances less than 50 ml per min should not be treated with this drug [25].

The results of clinical trials using topotecan in patients with malignant brain tumors are in Table 4 [37-40]. In these studies, myelosuppression was a significant complication and topotecan was found to have minimal activity in this setting. Because of excellent BBB penetration and the novel mechanism of action, other studies of topotecan in brain tumors are under way, including trials for such potentially chemosensitive tumors as oligodendrogliomas, brain metastases, and primary CNS lymphoma.

9-Aminocamptothecin (9-AC)

Hochberg conducted a phase I/II dose escalation study of 9-AC in 59 patients, 31 with newly diagnosed GBM and 28 with recurrent high-grade astrocytomas [8]. Although ineffective, the authors noted no grade III or IV myelosuppression in patients receiving concurrent "cytochrome P450 system inducing" AEDs. Although the trial was terminated, plasma levels of the drug may have been insufficient to achieve cytotoxic activity.

Alkylating Agents

Oxaliplatin

Cisplatin and carboplatin have been used both i.v. and intra-arterially as first-line chemotherapy for malignant glioma with survival rates similar to BCNU [41, 42]. However, significant myelosuppression (carboplatin) and nephrotoxicity (cisplatin) have limited the usefulness of these drugs. Oxaliplatin ([trans-(L)-1,2-*dia*minocyclo*hexane*] oxalatoplatinum (II)) is a cytotoxic platinum complex that has shown activity against colorectal cancer in combination and as a single agent in phase II and phase III clinical trials (Fig. 5) [43, 44]. Oxaliplatin's *dach* ring complex results in the formation of platinum-DNA adducts, which are more effective at blocking DNA replication than those formed by cisplatin. Because ototoxicity, nephrotoxicity, cardiac toxicity, and alopecia have not been observed in adults treated with oxaliplatin alone, this agent is an

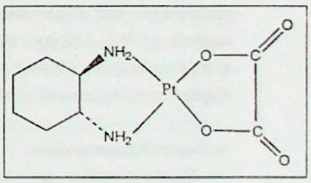

Figure 5. Oxaliplatin.

Table 4. Summary of clinical trials using topotecan in malignant gliomas

Author	Path	Study	# Patients	Dose	CR(%)	PR(%)	Remarks
Macdonald [37]	GBM (15) AA (16)	Ph-II Rec	31	1.5 i.v.; 5/21 d +	0 (0)	2 (6)	68% maintained stable disease.
Blaney [38]	GBM	Ph-II Rec	9	7.5 i.v.; 1/21 d *	0 (0)	0 (0)	Two patients maintained stable disease for 12 weeks and one for 16 weeks.
Eisenhauer [39]	GBM AA	Ph-II Rec	12	1.5 i.v.; 5/21 d +	1 (8)	1 (8)	—
Kyritsis [40]	GBM AA	Ph-II Rec	29	0.4 i.v.; 28 d cy *	0 (0)	3 (12)	15% of patients with stable disease.

CR = complete response; PR = partial response; Rec = recurrent; GBM = glioblastoma multiforme; AA = anaplastic astrocytoma; i.v. = intravenously; d = days; + 1.5 mg/m² daily on days 1-5 each 21-day cycle; * 5.5-7.5 mg/m² as a single 24-h continuous infusion on day 1 of each 21-day cycle; * Continuous i.v. infusion every 28 days with a starting dose of 0.4 mg/m²/day.

attractive candidate for use in brain tumors [45, 46]. The cumulative dose limiting toxicity in adults is sensory neuropathy (12%). In those patients who developed sensory neuropathy of grade 2 or higher, symptoms regressed in 82% at four months and completely resolved in 41% at eight months after the drug was discontinued [45].

Experience with oxaliplatin for treatment of malignant gliomas is limited. *Misset* reported a PR in two of six patients (33%) with GBM [47]. *Soulie* reported a complete response (CR) in one of nine patients (11%) with recurrent GBM [48]. Both of these series incompletely defined pretreatment status and patient outcomes and used varying dosages of oxaliplatin. A phase II trial of neoadjuvant oxaliplatin at 130 mg/m^2 every three weeks is planned for newly diagnosed GBM.

Biological Agents

Protein Kinase C Inhibitors

Protein kinase C (PKC) is a phospholipid-dependent, cytoplasmic, serine threonine kinase responsible for signal transduction in response to various growth factors, hormones, and neurotransmitters. Once activated, PKC phophorylates proteins and triggers many cellular responses including membrane transport, gene expression, and cellular differentiation/proliferation [49]. PKC inhibition has been investigated as a therapeutic strategy for malignant gliomas because of its critical intermediary role in the malignant transformation, proliferation, and invasiveness of glial cells [50, 51]. Two methods of PKC inhibition that have been studied in clinical trials for malignant gliomas are i.v. treatment with antisense oligonucleotides and oral tamoxifen.

Antisense Oligonucleotides

Oligonucleotides are short sequences of nucleotides (usually at least 15 bases in length) designed to hybridize with complementary messenger RNA (mRNA) and prevent translation of the RNA message at the ribosome (Fig. 6). Unmodified oligonucleotides are unstable in the circulation primarily due to degradation by ubiquitous cellular nucleases, and have a half-life of about five min [52]. Substituting one of the oxygens in the phosphate groups with a sulfur atom (phosphorothioate modification) makes these fragments (S-oligos) resistant to cleavage, increases the half-life to approximately one hour, and allows for continuous i.v. infusion. Upon administration, S-oligos are presumed to enter cells by endocytosis [53].

ISIS 3521 is a phosphorothioate oligonucleotide that binds to the 3′ untranslated region of PKC mRNA with high affinity and inhibits the production of protein kinase C-ax, a PKC isoenzyme, by promoting cleavage of the hybridized molecule [54]. ISIS 3521 is the subject of an ongoing phase II trial for treatment of recurrent malignant glioma.

There are several potential limitations associated with the systemic administration of antisense oligonucleotides. First, the delivery of antisense compounds to tumor cells beyond an intact BBB may be impeded due to the highly negative charge, acid lability, and large molecular weight of S-oligos [55]. Second, this therapeutic compound accumulates in the liver, kidneys, and throughout the reticuloendothelial system and relatively small amounts may be left to traverse the BBB and enter the tumor. Continuous i.v. infusion may be necessary to achieve sufficient and sustained delivery of antisense oligonucleotides to the tumor [52]. Effective treatment of tumor cells exhibiting cell-cycle dependent susceptibility to an antisense compound (depending on the molecular target) may require this delivery method. Third, multiple genes are important in cell proliferation, invasiveness, and survival. Targeting PKC alone may not result in cytotoxicity or sustained tumor response. Finally gene expression changes over time and blocking one critical cell pathway may activate yet another. Some of these limitations may be bypassed by direct tumoral infusion.

Tamoxifen

Tamoxifen is an agent widely used for adjuvant treatment of breast carcinoma. When administered in sufficient doses, tamoxifen yields an estrogen receptor-independent antineoplastic effect by inhibiting PKC [56]. Tamoxifen also induces transforming growth factor beta 1 and inhibits ouabain-sensitive Na-K ATPase, Mg-ATPase, calmodulin dependent protein kinase, and certain calcium channels [57, 58]. The clinical relevance of these mechanisms has not been fully defined.

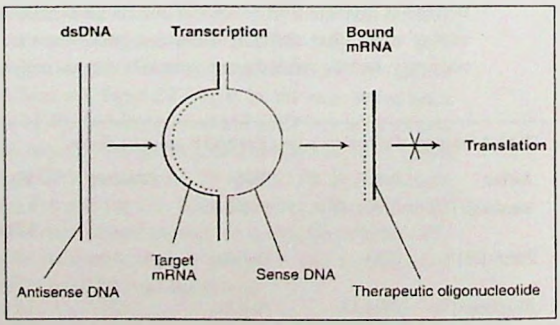

Figure 6. Antisense RNA. Antisense oligonucleotides bind the target to the messenger RNA (mRNA) sense strand, thus blocking successful translation of the corresponding protein. High-affinity binding (formation of the RNA duplex) results in gene inactivation either through steric blocking of the ribosome complex or by triggering mRNA cleavage by RNase H. This diagram presumes that the target gene is regulated by transcription from the sense RNA strand.

Table 5. Summary of clinical trials using tamoxifen in recurrent malignant gliomas

Author	Path	Study	# Patients	Dose	Med Survival*	Remarks
Vertosick [59]	GBM (29) AA (3)	Ph-I	32	20 mg p.o. BID	17 wks KPS ≤ 60 8 wks KPS ≥ 70 21 wks	7/32 pts remained stable on tamoxifen for >6 mos.
Couldwell [60]	GBM (6) AA (5)	Ph-I	11	160-200 mg p.o. daily	24 wks	PR in three pts—these responders survived longer than 12 mos with clinical improvement.
Vertosick [61]	GBM (53)	Ph-I	26 18 9	40 mg p.o. daily 80 mg p.o. daily 160 mg p.o. daily	12 wks 18 wks Not reached at time of publication	Significant reduction in peritumoral edema.
Freeman [62]	Brain stem gliomas (5)	Anecdotal	5	Not reported	Not reported	PR in 4/5 pts. SD in one pt. Remissions of up to 26 mos.
Couldwell [63]	GBM (20) AA (12)	Ph-II	32	80 (F)-100 (M) mg p.o. BID	GBM 29 wks AA 64 wks	PR in four AA and four GBM pts with SD in six as measured by MRI and PET.
Pollack [64]	GBM/AA	Ph-I	7 7	60 mg p.o. BID 100 mg p.o. BID	11 wks	SD in four pts for at least three months. Longest survivor was 17 months.

*After initiation of therapy.
Pts = patients; Ph = phase; PR = partial response, SD = stable disease; GBM = glioblastoma multiforme; AA = anaplastic astrocytoma; p.o. = orally; mos. = months; wks = weeks; M = male; F = female; KPS = Karnofsky Performance Status; PET = positron emission tomography.

Because of the sensitivity of glioma cell lines to tamoxifen-induced PKC inhibition, this drug has been the subject of several clinical trials (Table 5) [59-64]. These trials have enrolled patients with largely inoperable, recurrent malignant gliomas. Median survivals have ranged from 11-64 weeks from the initiation of tamoxifen therapy with partial radiographic responses varying widely between series (0%-80%) [65].

There appears to be a consistent relationship between higher tamoxifen doses, higher radiographic response rates, and longer survival [61]. This is exemplified by *Couldwell's* description of a 49-year-old male with recurrent glioblastoma treated with tamoxifen 20 mg orally twice a day [60]. Six weeks later, progressive disease was documented on brain MRI and the patient was then treated with tamoxifen 100 mg orally twice a day. This resulted in clinical improvement, a radiographic PR, and a greater than nine-month survival.

Micromolar concentrations of serum tamoxifen can be achieved within several days by "loading" with 1,000 mg per day prior to the administration of the maintenance dose [64]. Tamoxifen has been shown to attain high concentrations in brain metastases and surrounding brain tissues in patients with breast cancer [66]. Levels of tamoxifen within the middle of the in vitro therapeutic range have also been demonstrated in a tumor biopsy specimen from a patient with malignant glioma treated with this drug [60].

PKC inhibition for the adjuvant treatment of malignant gliomas is a strategy still under investigation. Another PKC inhibitor under development is staurosporine. This drug is more effective at halting the proliferation of glioma cell lines at lower does than tamoxifen [67]. Clinical trials with this agent have not yet been reported.

Cell Signal Transduction Inhibitors

Peptidomimetic drugs developed to target critical intermediaries in cell signal transduction pathways represent another novel class of antineoplastic drugs. The main focus has been on inhibiting ras, a family of GTP-binding cytoplasmic proteins with a pivotal role in the development and progression of many human cancers (Fig. 7). Permanent activation of the ras-signaling pathway requires insertion of proteins into the plasma membrane. This in turn requires attachment of a farnesyl group (15 carbon lipid tail) to the protein, a reaction catalyzed by the enzyme, farnesyl transferase. Inhibition of this step by a farnesyl transferase inhibitor (FTI) is a potentially useful antineoplastic strategy [68, 69]. In animal models, tetrapeptide FTIs specific for ras have successfully interrupted the transmission of signals from activated cell surface growth factor receptors to downstream intracellular partners. FTIs are cytostatic and have demonstrated in vitro activity against a number of human tumor cell lines.

There is a sound rationale for the study of FTIs in malignant gliomas, as up to 70% of these tumor specimens overexpress ras oncoproteins [70]. Moreover, ras-dependent receptors (epidermal growth factor receptor, platelet-derived growth factor/receptor, and insulin growth factor/receptor-1) have been implicated in brain tumorigenesis [71]. Finally, because FTIs are cytostatic and known to have synergistic effects on tumor cell lines when used in conjunction with standard chemotherapeutic agents, the most effective clinical application of these drugs may be as part of a multiple drug combination [72].

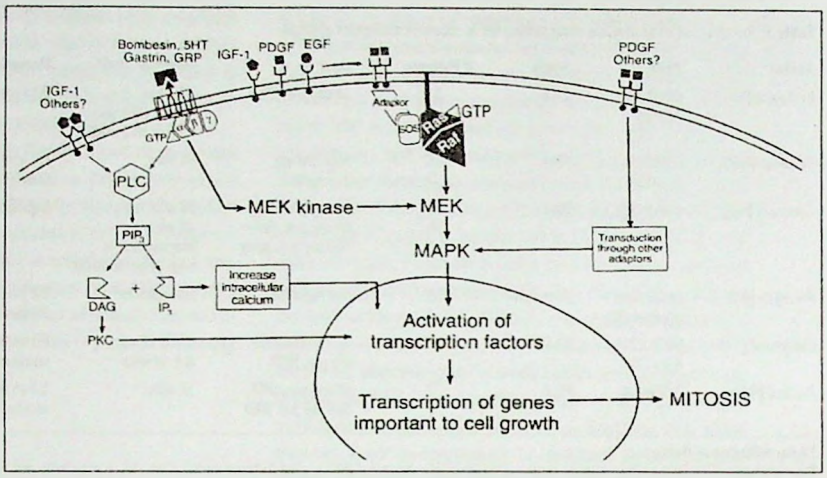

Figure 7. Cell signal transduction. *Ras is illustrated attached to the plasma membrane by a farnesyl anchor. This protein occupies a pivotal position in cellular replication. However, some ras-associated receptors such as PDGF are known to act via multiple pathways. The existence of multiple parallel pathways of signal transduction is a theoretical limitation of farnesyl transferase inhibitors as antineoplastic therapy. Used with permission from [68].*

Immunotherapy

Cytokines

Interferons possess direct tumor cytotoxicity and a capacity for immune modulation. They may act indirectly to recruit and activate leukocytes, augment expression of cell surface molecules, and induce the production of other intermediate cytokines. Studies have demonstrated that human interferon alpha and beta inhibit tumor growth in rodent glioma models, and a large number of phase I and II clinical trials investigating these interferons have been reported over the past decade [73-76]. Limitations of these studies have included selection bias, inadequate sample size, and incompletely documented progression-free survival and radiographic response rates. Despite these shortcomings, other groups have reported encouraging response rates and survival times [77-79].

Rajkumar reported results of a phase I study evaluating radiation combined with recombinant interferon alpha-2A and BCNU as initial therapy for patients with high-grade glioma [80]. Five of nine patients evaluable for radiographic response had a PR, with a median survival of the entire cohort approaching four years. In a phase II study evaluating alpha interferon and BCNU for patients with recurrent high-grade glioma, *Brandes* reported on 21 patients who had not received prior chemotherapy [81]. A PR was obtained in 7/21, and 6/21 maintained stable disease, although overall median survival was seven months. Both of these studies reported "substantial but acceptable" constitutional symptoms.

Adoptive Immunotherapy

The cellular immune response in malignant glioma patients is significantly depressed as demonstrated by impaired blastogenic response of peripheral blood lymphocytes and reduced interleukin 2 (IL-2) production and IL-2 receptor expression of mitogen-stimulated T cells. Peripheral blood lymphocytes from glioma patients can be activated in vitro by IL-2, and these lymphokine-activated killer cells (LAK cells) are capable of killing both autologous and allogenic glioma cells [82].

Hayes treated 15 recurrent malignant glioma patients with intracavitary LAK cells and IL-2 in six-week cycles through a modified Ommaya reservoir placed at the time of reoperation [83]. Four radiographic responses (two CR and two PR) and a median survival of 53 weeks after reoperation were reported. Eight of these patients survived more than one year. These data should be interpreted cautiously as some patients received surgery and/or chemotherapy subsequent to LAK/IL-2 administration.

Plautz reported 10 patients with progressive primary or recurrent malignant glioma who were treated with systemic T cell adoptive immunotherapy [84]. These patients were vaccinated with irradiated autologous tumor cells, and T cells from draining inguinal lymph nodes were then harvested, stimulated, and expanded. Following i.v. T cell transfer therapy, radiographic regression that lasted at least six months was demonstrated in two patients with recurrent tumors, and one patient demonstrated stable disease that lasted more than 17 months. Four of eight patients with recurrent tumor were alive more than one year after surgery for recurrence.

The source, specificity, and number of T cells are essential determinants of efficacy. There are significant limitations of this treatment strategy. First, diminished immune responses are generated against antigens introduced into the CNS. Second, the BBB effectively impedes T cells from reaching

their target. Third, many gliomas release substances such as tumor growth factor β and IL-10 that cause immunosuppression. Finally, the brain might not tolerate the inflammation associated with an immune reaction [84].

Gene Therapy

Gene therapy is an attractive strategy for the treatment of brain tumors because of the lack of systemic toxicity and the ease of application during stereotactic procedures or craniotomy. Direct introduction of genes without any cellular or viral vector can be accomplished via aerosol, systemic delivery, or microcellular injection. Indirect gene delivery by transplantation of genetically engineered cells or inoculation of a recombinant defective virus is more clinically relevant and constitutes a highly efficient means of transferring DNA to a target cell [85].

The most common experimental paradigm for genetic treatment of brain tumors has been delivery of the herpes simplex virus thymidine kinase (*HSV-tk*) gene to the tumor using an adenovirus vector (Fig. 8). Adenoviruses are highly stable, nonenveloped, double-stranded DNA-containing viruses with a low rate of genomic instability and, therefore, low risk of insertional mutagenesis. Adenoviruses transfer their DNA by binding to a specific cell surface receptor, entering the cytoplasm by endocytosis, and then forming a pore in the endosome to translocate genetic material to the nucleus [86].

In principle, the HSV-tk construct should only be delivered to dividing cells (i.e., tumor cells and not neurons). The thymidine kinase that is being produced by these cells can phosphorylate nucleoside analogs such as ganciclovir to form nucleotide-like precursors that will block replication of DNA. Although the transduction process alone is not cytotoxic, cellular production of thymidine kinase confers susceptibility to those cells subsequently exposed to ganciclovir. The so-called "bystander effect" is the result of diffusion of phosphorylated nucleosides away from dying cells to adjacent nontransduced tumor cells resulting in their death [86].

Ram treated 15 patients with recurrent malignant brain tumors using intratumoral injection of murine cells modified to produce retroviral vectors containing the HSV-tk construct [87]. Nine of these 15 patients had GBM and were treated to either a single focus or multiple foci of disease. Three of the nine patients exhibited either a CR or PR, with smaller lesions most likely to respond. Potential limitations of this strategy include lack of transduction of distant tumor cells, transduction of endothelial cells, and immunologic rejection of the murine vector cells.

Izquierdo used retrovirus-mediated gene therapy to treat five patients with anaplastic glioma and two of these patients showed a PR [88]. In a follow-up study the investigators reported that they had been unable to reduce the tumor size of recurrent glioblastoma patients with tumor volumes larger than 100 cm^3 by applying the standard HSV-tk/ganciclovir therapy or to prolong patient survival for more than eight months [89]. These observations underscore the need for more effective delivery and distribution strategies.

Ideally, gene therapy with a replication-competent adenoviral vector should result in intracellular viral replication and exclusive cytolysis of targeted cancer cells. In theory, newly released virions from a lysed cell could then infect both neighboring and distant cells but selectively replicate only in cancer cells. ONYX-015 (dl1520) is an adenovirus construct designed to be differentially lethal to tumor cells with mutated or deleted *p53*, a tumor suppressor gene important in the early transformation of most gliomas [90].

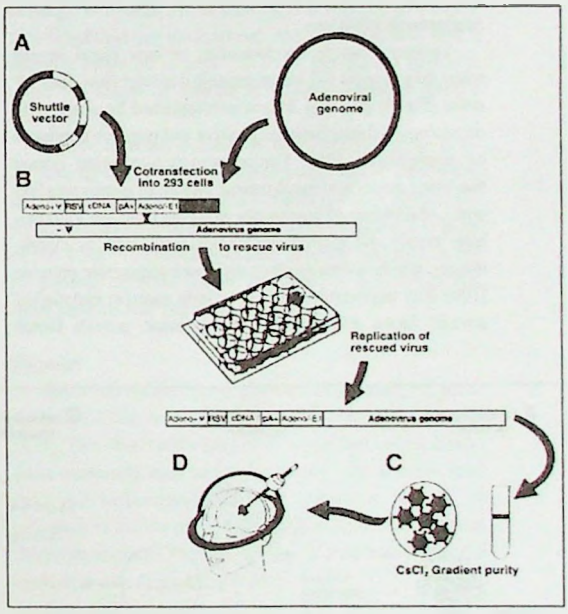

Figure 8. Gene therapy. *A) The shuttle vector containing the expression cassette with the foreign gene of interest is cotransfected with the plasmid containing the adenoviral genome. B) The vector containing the adenovirus genome is missing the packaging sequence and cannot produce virus. The shuttle vector also cannot replicate and produce virus because it is missing a large piece of the adenoviral genome. For virus production, the shuttle vector containing the packaging sequence and the expression cassette must recombine with the adenovirus genome. C) The recombinant virus can replicate in human embryonic kidney 293 cells. Replicating virus is easily identified by the lysis of cells in tissue culture. After growth and plaque purification, large quantities of recombinant adenovirus can be processed over a cesium chloride density gradient. D) After dialysis, replication-defective adenovirus can be used for in vivo transfections. Used with permission from [86].*

A key feature of the ONYX construct is the genetic deletion of an adenoviral protein (E1B 55K) that binds to the N-terminus of *p53* and blocks its activity. Since E1B 55K is deleted in this construct, the cellular *p53* system can respond to "therapeutic" infection by promoting cell-cycle arrest in *p53*-positive cells (a nonlethal infection) or cytolysis in *p53*-negative cells [91]. Initially encouraging cell line and animal study results using ONYX-015 virus have been tempered, however, by recent reports of wild-type *p53* dependent cytolysis [92-95]. *Fueyo* has also demonstrated that overexpression of E2F-1, a promoter of inappropriate cell entry into the S-phase that is upregulated by ONYX-015, triggers apoptosis and suppresses tumor growth in vitro and in vivo independently of cellular *p53* status [96]. These new data suggest that molecular mechanisms concerning replication competent adenoviral vectors need to be defined prior to use in a clinical setting.

Angiogenesis Inhibitors

Tumors promote the formation of new blood vessels when they surpass 1-2 ml in greatest diameter (less than 10^6 cells) (Fig. 9) [97, 98]. This is accomplished by altering the physiologic balance between positive and negative regulators of angiogenesis [99]. Tumor neovascularization occurs through a number of mechanisms including overexpression and mobilization of angiogenic proteins from the extracellular matrix and recruitment of host cells such as macrophages, which in turn produce their own angiogenic proteins [100]. Key angiogenic proteins include vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), and tenascin. Endogenous inhibitors of angiogenesis include angiostatin, endostatin, and thrombospondin [101].

When the angiogenic process is triggered, a cascade of events including activation of endothelial cells, proteolytic degradation of the extracellular matrix and basement membrane, proliferation and migration of endothelial cells, endothelial tube formation, and fusion/reassembly of the extracellular matrix occur [102]. Vascular basement membrane degradation allows endothelial cells to migrate into the surrounding tissue and form vascular structures [103]. The basement membrane consists of both fibrous and nonfibrous proteins including heparan sulfate proteoglycans, which can bind and enable growth factors such as bFGF and VEGF [104]. This complex degradative process involves many enzymatic systems that result in the release of stored growth factors and, in turn, promote further angiogenesis. Matrix metalloproteinases, serine proteases (plasminogen activators), and cathepsins are among the enzyme classes implicated in this process [105].

Most experience with antiangiogenesis treatments in brain tumors has been with matrix metalloproteinase inhibitors (MMPIs). The MMPs are a family of over a dozen secreted and membrane-bound zinc endopeptidases. They require activation by other proteolytic enzymes in order to digest an extracellular matrix. MMPs are upregulated in primary and metastatic brain tumors and correlate with malignant progression [104, 106]. One of the MMPs, MMP-9, is thought to play a critical role in

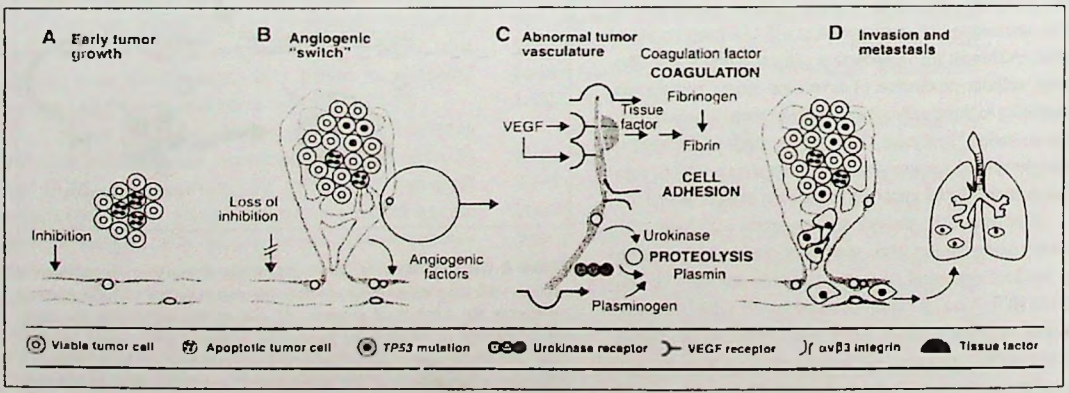

Figure 9. Tumor angiogenesis. A) Small tumor, less than 1 mm³ in diameter with high rate of apoptosis, cannot grow further without new blood supply. B) Hypoxic environment and genetic instability allow evolution of tumor clones with loss of p53 *function. These cells have lower apoptotic rate, and produce angiogenic factors, inducing new vasculature (angiogenic "switch"). There is also reduction in antiangiogenic factors. C) Tumor vasculature is abnormal. Leaky vessels allow passage of fibrinogen, and tissue factor is expressed on tumor endothelium producing fibrin deposits. VEGF receptors and urokinase receptor integrins are upregulated. Endothelial cells are dividing. D) These processes allow invasion and metastasis to distant sites. Used with permission from [101].*

tumor cell invasion, and, in one study, was detected in the CSF of patients with brain tumors but not in control patients [103].

Marimastat is an orally available MMPI that blocks the ability of tumor cells to disrupt the extracellular matrix, prevents the ingrowth of new blood vessels, and inhibits glial tumor growth and spread in animal cancer models [107]. A multicenter phase III trial of Marimastat in recurrent malignant gliomas has recently been completed.

Thalidomide is an antiangiogenic agent that decreases the expression of beta integrin subunits produced by leukocytes. Because these integrins are crucial for cell-matrix interactions, thalidomide is felt to inhibit cell migration accounting for its antiangiogenic (and teratogenic) activity [108]. Its clinical utility as a long-term treatment for malignant gliomas remains under investigation. *Yung* reported findings from a phase II trial of the antiangiogenic agent thalidomide in patients with recurrent high-grade gliomas [109]. Of the 32 evaluable patients, there were two PRs, two minor responses, and a median time to progression of eight weeks. The assessment of cytostatic antiangiogenesis agents as potential treatments for malignant glioma poses significant challenges in clinical trial design, as discussed earlier in **Clinical Trial Design**.

Delivery Strategies

RMP-7

The BBB impedes passage of circulating compounds that are hydrophilic, ionized, greater than 18 Å in diameter, or more than 180 Da in molecular weight [110]. This excludes many conventional chemotherapy drugs such as cyclophosphamide and the anthracyclines. As the integrity of the BBB is partially compromised in brain tumor-associated blood vessels, it is controversial whether hydrophilic drugs have difficulty traversing this physiologic barrier. However, restoration of the BBB by coadministration of corticosteroids may impede delivery of these agents [111]. Mannitol disruption of the BBB was described almost two decades ago and continues to be a technically difficult method used for the delivery of high-dose chemotherapy [112]. More recently, RMP-7, a bradykinin analogue, has been developed to transiently increase BBB permeability while avoiding some of the risks inherent with the mannitol procedure.

RMP-7 stimulates endothelial B2 receptors, which results in intracellular calcium influx, contraction of capillary endothelial cells, and loosening of tight junctions [113]. In addition, RMP-7 increases vesicular transport and transcellular penetration. These effects led to increased permeability of the BBB in animal studies with lanthanum, a 139 molecular weight tracer substance [114]. RMP-7 has a longer plasma half-life than bradykinin although it exerts its effects over a narrow time frame so that the timing of chemotherapy administration in relation to RMP-7 is critical [115]. RMP-7 preferentially "opens" the BBB in the tumor area [116]. Despite this, vasogenic edema as an adverse event rarely occurs unless serum proteins extravasate into the brain parenchyma. Transient decreases in arterial blood pressure have been observed with high-dose RMP-7 administration in a swine model, but the drug appears to be well tolerated otherwise [113].

The infusion of intracarotid RMP-7 followed by carboplatin in a rat glioma model produced longer survival than in those rats treated with carboplatin alone [115]. The amount of carboplatin used in this experiment was substantially less than an equivalent i.v. dose in humans. RMP-7 also increased permeability to carboplatin in dexamethasone-treated tumors although to a lesser extent than rats not exposed to steroids. In an irradiated dog brain model, RMP-7 appeared to have a selective effect on an impaired BBB, but did not appear to affect the extent or volume of radiation-induced cerebral edema [117].

Gregor reported preliminary data from two phase II trials investigating RMP-7 administered with i.v. carboplatin in recurrent malignant glioma patients [118]. A statistically significant survival hazard ratio of approximately 2 in favor of the RMP-7/carboplatin-treated patients was seen in the 87 patients enrolled. There was also an implication that these patients had improved QOL.

Polymers

Since 90% of malignant gliomas recur within 1-2 cm of the original site, local therapy may be an effective strategy [119]. This observation has served as the basis of focal radiation treatments such as brachytherapy, proton beam therapy, and radiosurgery. Another method is the use of polymers to deliver drugs via diffusion from micropores in the polymer matrix or by the release of drug from within the interstices of a degradable matrix.

One BCNU polymer design is a 1.45-cm diameter wafer disk that consists of a biodegradable polymer component (poly bis(p-carboxyphenoxy) propane and sebacic acid or PCPP-SA) uniformly impregnated with 7.7 mg of BCNU (1,3-bis (2-chloroethyl)-1-nitrosourea). The usual dose is eight wafers, which are to be placed in the margins of the surgical resection cavity. BCNU is released from the wafer over two to three weeks and subsequently diffuses into surrounding brain tissue to produce an antineoplastic effect by alkylating DNA and RNA [120].

Although comparable human data are lacking, recent work by *Fung* with intraparenchymal BCNU impregnated

polyanhydride pellets in cynomolgus monkeys revealed high drug levels (0.5-3.5 mM) within 3 mm of the implant over a period of approximately one month [121]. Pharmacokinetic studies demonstrated that BCNU area under the concentration time curve (AUC) was 4-1,200 times higher than the AUC achieved with i.v. administration of a higher dose. The applicability of this animal study is unclear.

In a randomized, double-blind, placebo-controlled clinical trial in adults undergoing surgical resection for recurrent malignant glioma, 222 patients were assigned to receive surgically implanted biodegradable polymer disks with or without 3.85% BCNU (by weight) [122]. Among patients with glioblastoma, treatment with placebo polymer resulted in 64% mortality at six months, compared to a 44% six-month mortality for those treated with the BCNU polymer ($p = 0.02$). Limitations of this study include the fact that no survival advantage was shown over historical controls treated with i.v. BCNU, BCNU polymer produced no survival prolongation in patients with pathologic diagnoses other than GBM, and maximal feasible resection and initial KPS were strong predictors of survival irrespective of treatment with the BCNU implants. Furthermore, the clinical relevance of the six-month comparison is questionable. Follow-up data demonstrated no significant difference in survival between BCNU polymer and placebo groups at approximately 40 weeks. Dose-escalation trials incorporating wafers with higher concentrations of BCNU by weight are ongoing.

A prospective, randomized, double-blind study of BCNU polymer versus placebo at the time of initial surgery for malignant gliomas was recently reported by *Valtonen* [120]. All 32 patients in the study received involved field radiation therapy following surgery. For 27 patients with grade IV tumors, the median time from surgery to death was 40 weeks for the placebo group and 53 weeks for the active treatment group ($p = 0.008$). The two-year survival for patients receiving BCNU polymer was 30% as compared to 6% in the placebo-controlled polymer patients. Adverse events in the BCNU polymer arm were relatively few. These results should be interpreted with caution as the original study planned to enroll 100 patients and was stopped prematurely due to administrative issues; there were more AAs in the BCNU polymer arm; and there was no comparison to i.v. BCNU.

Many other chemo- and immunotherapies are being developed for interstitial delivery [123, 124]. Carboplatin is one such candidate that has shown activity against gliomas when administered i.v. but has limited use because of myelotoxicity. Carboplatin polymer was implanted in an experimental glioma rat model [125]. In this setting, median survival increased threefold over controls and it was shown that the best intracranial polymer dose was significantly more effective than the best systemic dose tested. Similarly with cisplatin, mean survival was significantly prolonged as compared to control animals and animals treated with placebo polymer. At autopsy no evidence of viable tumor was noted in the animal survivors [126]. The relevance of these animal models to human glioma patients remains uncertain.

Conclusion

Malignant gliomas remain a poorly understood form of cancer associated with high rates of morbidity and mortality. Nevertheless, prospects for the future are better than ever before. Developments in molecular biology have led to a clearer understanding of the mechanisms of tumor development, growth, and resistance to therapy. As a result, new treatment strategies are emerging that target steps in the molecular pathogenesis of these tumors. Antiangiogenesis agents, antisense oligonucleotides, and signal transduction inhibitors are all examples of such therapies now entering clinical trials. Improved cytotoxic agents that penetrate the BBB (topoisomerase I inhibitors, temozolomide, oxaliplatin) are other promising therapeutic agents. Finally, strategies to circumvent the BBB (polymers, bradykinin analogues, gene therapy) are important advances that have also shown efficacy in early clinical trials. Future treatment strategies for malignant gliomas will likely involve synergistic combinations of agents aimed at different pathways in the molecular pathogenesis of this type of cancer.

The pace and breadth of discovery in molecular biology promise a steady supply of novel agents as well as refinements of existing ones. One of the important challenges for the future is the development and implementation of sound clinical research methods that will enable investigators to identify active treatment regimens. Although the traditional outcomes of survival and time to progression remain important, incorporation of neuropsychological outcomes and valid, reliable QOL instruments assume great importance for future studies. Extending and improving QOL should be the complementary goals of any new agent for malignant gliomas.

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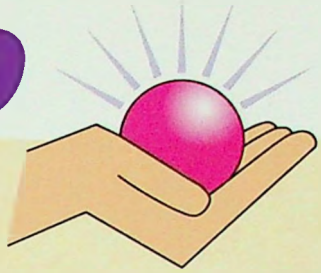
Cantop

Topotecan Hydrochloride 2.5 mg.

...providing solutions



ABRIDGED PRODUCT INFORMATION

Presentation : Each carton of Cantop contains:

One single dose vial of Cantop
Composition: Topotecan Hydrochloride : 2.5 mg
in Lyophilized powder form.

One ampoule of water for Injection
Composition: Water for Injection q.s. to 2.5 mg
For reconstitution during administration.

Indications:
Cantop (Topotecan Hydrochloride) is indicated in the treatment of:
* Metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy.

* Small cell lung cancer sensitive disease after failure of first line chemotherapy. In clinical studies submitted to support approval, sensitive disease is defined as disease responding to chemotherapy but subsequently progressing after atleast 60 days (in the phase III study) or atleast 90 days (in the phase II study) after chemotherapy.

Contraindications: Cantop (Topotecan Hydrochloride) is contraindicated in patients with hypersensitivity to Cantop (Topotecan Hydrochloride). Its usage is not recommended during pregnancy or lactation. It is also contraindicated in patients with severe bone marrow depression.

Dosage: Cantop (Topotecan Hydrochloride) is intended for use only as an intravenous infusion after reconstitution and dilution. The recommended dose is 1.5 mg/m^2/day administered as intravenous infusion over 30 minutes, for 5 consecutive days. This cycle should be repeated after 3 weeks starting from day 1 for minimum of 4 cycles. In the event of severe neutropenia, the dose should be reduced by 0.25 mg/m^2/day, in subsequent cycles. Alternatively administration of G-CSF may be considered to regulate the severity of myelosuppression.

Mode of action : Cantop (Topotecan Hydrochloride), an antineoplastic agent, is a semisynthetic derivative of camptothecin and is topoisomerase I inhibitor, an enzyme which relieves torsional strain during DNA replication. The cleavable complex normally formed between DNA and topoisomerase I is stabilised by Topotecan, with resultant breaks in single stranded DNA.

Pharmacokinetics: Cantop (Topotecan Hydrochloride) undergoes a reversible pH dependant hydrolysis in its lactone moiety which is biologically active, into inactive hydroxy acid form. The peak plasma concentration and the area under plasma concentration versus time curves (AUC) show linear relationship with increasing dosages. No evidence of drug accumulation is seen with daily 30 minute infusions for five consecutive days. The mean total body clearance of the lactone form is 30 L/h/m^2, with a mean elimination half-life of 3 hours. Renal clearance accounts for approximately 40% of the dose administered with large inter individual variability. Renal dysfunction may decrease topotecan plasma clearance. Creatinine clearance is significantly, but poorly correlated with Cantop (Topotecan Hydrochloride) clearance. Hepatic impairment does not appear to influence the Cantop (Topotecan Hydrochloride) disposition.

ADVERSE REACTIONS:

Haematological Reactions: Myelosuppression characterised primarily by neutropenia is dose limiting toxicity in therapy with Cantop (Topotecan Hydrochloride). Grade-IV neutropenia may occur in a majority of cases, during first course of administration. In subsequent courses , the incidence may come down to some extent but requires attention of the clinician. The nadir neutrophil count may be encountered between day 8-11. However, neutropenia associated with Cantop (Topotecan Hydrochloride) therapy is non-cumulative in nature. Febrile neutropenia occuring in few patients may require hospitalisation.

Thrombocytopenia is also encountered in moderate number of patients receiving Cantop (Topotecan Hydrochloride) therapy. The nadir count is usually observed between day 10-15. In few cases, platelet transfusion may be necessitated.

Severe anaemia amounting to haemoglobin < 8 gm/dL may also be observed in patients receiving Cantop (Topotecan Hydrochloride) therapy.

Warning and Precautions: Prior to the first course of Cantop (Topotecan Hydrochloride), patients must have a baseline neutrophil count of > 1500 cells/ mm^3 and a platelet count of 100000 cells/ mm^3. Peripheral blood a counts should be monitored regularly during therapy with Cantop (Topotecan Hydrochloride).

Stability: Unopened vials of Cantop (Topotecan Hydrochloride) are stable until the date indicated on the package when stored between 20° and 25° C. As the vials contain no preservative, contents should be used immediately after reconstitution.

Reconstituted vials of Cantop (Topotecan Hydrochloride) diluted for infusion are stable at approximately 20° and 25° C and ambient lighting condition for 24 hours.

Cantop

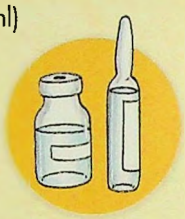
Topotecan Hydrochloride 2.5 mg.

...providing solutions

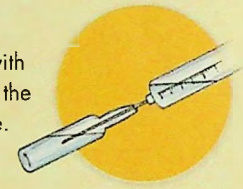
PREPARATION FOR ADMINISTRATION

RECONSTITUTION:

(A) Preparation of Cantop premix soln.
(Topotecan 2.5 mg/2.5ml)



A-1 Take out the Cantop vial and Water for injection (WFI) ampoule from the carton.



A-2 Using a syringe fitted with needle aseptically withdraw the entire WFI from the ampoule.

A-3 Inject the entire content of syringe into the Cantop vial.

A-4 Remove the syringe and needle and shake the mixture manually for 15 seconds or till the lyophilized powder dissolves in the WFI.

A-5 This premix solution contains 2.5mg/2.5 ml (1.0 mg/ml) Topotecan.

DILUTION:

(B) Preparation of the Infusion solution.

B-1 Based on the required dose of the patient expressed in mg, aseptically withdraw the premix solution using a graduated syringe fitted with needle.

B-2 Inject the required premix solution into the infusion bag or bottle containing either 5% dextrose solution or 0.9% sodium chloride (normal saline) solution.

B-3 The final concentration of infusion solution should be between 25 to 50 mcg/ml (For example a 2.5 mg solution can be diluted to 100 to 50 ml). Shake the infusion bag or bottle using a rocking motion.

Administration : The Cantop (Topotecan Hydrochloride) infusion solution should be aseptically administered intravenously immediately after preparation as a 30 minutes infusion under room temperature and normal lighting condition.

For further information please write to: Cantop Cell, Dr. REDDY'S LABORATORIES LTD.,
8-2-337, Road No. 3, Banjara Hills, Hyderabad 500 034. Phone: 049-3358471; Fax: 040-3358472; email: drlpmt@hotmail.com

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HAZARD SYMBOLS

For your safety and as a precautinary measure, we strongly recommend that all of our products should only be handled by qualified individuals knowing proper handling procedures of the chemicals listed and familiar with their potential hazards. Certain chemicals are extremely harmful, toxic and/or otherwise hazardous in nature

Hazard Symbols and Risk warnings are displayed on our Product Lables in accordance to the International Rules & Procedures practised. The absence of a warning must not be interpreted as an indication of safety. Therefore, in all circumstances users should check whether additional precautions are necessary

FLAMMABLE		Hazard : 1. Spontaneously falmmable substances. 2. Highly flammable gasses. 3. Substances sensitive to moisture. 4. Flammable liquids (with flash point below 21°C) Caution : Store in cool places. Keep away from open flame, source of heat and sparks.
EXPLOSIVE		Hazard : This symbol designates substances which may explode under definite conditons. Caution : Avoid shock, friction, sparks and heat.
TOXIC		Hazard : The subsances are very hazardous to health when breathed, swallowed or in contact with the skin and may even lead to death. Caution : Avoid contact with the human body and immediately consult a doctor in cases of malaise.
CORROSIVE		Hazard : Living tissues as well as equipment are dstroyed on contact with these chemicals. Caution : Do not breathe vapours and avoid contact with body and clothing.
IRRITANT		Hazard : This symbol designates substances which may have an irritant effect on skin, eyes and respiratory organs. Caution : Avoid inhalation and direct contant with the body.
HARMFUL		Hazard : Inhalation, ingestion and continues exposure of skin by these chemicals is harmful. Caution : Avoid inhalation and direct contact with human body.
OXIDIZING		Hazard : Oxidising substances can ignite combustible material or worsen existing fires and thus make fire-fighting more difficult. Caution : Keep away from Air and moisture.

General Conditions of Sale

All sales and transactions entered into by Lab & General Exports (P) Ltd ("Seller) for "T. Baker" Brand of Lab chemicals and reagents shall be subject to the following general conditions of sale except where other specific terms have been agreed. The terms and conditions as stated herein are subject to change.

Issuing purchase order for the seller's products will be considered as buyer's consent to the seller's terms and conditions, irrespective of the buyer's own conditions of purchase.

ORDERS

For all orders accepted, seller's will arrange prompt despatch. For items which may not be readily available, sellers will intimate the probable delivery schedule and if acceptance to the buyer, despatch would be made accordingly. The sellers reserve the right to refuse the acceptance of order where (a) delivery may not be possible due to transportation barriers (b) items ordered may not be available in ready stock and are in short supply (c) restrictions have been imposed by authorities for export and or import by respective countries of despatch/destination.

PRICES

All prices indicated in our price list are wholesale. All prices are quoted in American dollars. All prices are exclusive of Frieght, packing any tax, customs duty, import tariff, value added tax. Prices quoted in this list are subject to fluctuation without notice. The seller's reserve the right to accept the order at their own discretion and to invoice the goods at the prevailing prices on the date of delivery/dispatch. Any UN specified or DOT USA special packaging will be added extra to the buyers account. Our stockists, agents and dealers are free to resell the goods at their own prices.

QUOTATIONS AND ORDER ACCEPTANCE

For all enquiries and requests received, the seller will provide quotations as per prices ruling. Quotations can also be provided for non-listed items, bulk quantities and bulk packings. Orders received by telephone, fax or electronic data exchange shall be binding only after we have issued written confirmation of the same. The seller will accept orders from government, educational and commercial organisations only. Orders placed by private individuals shall not be entertained. We reserve the right to deliver/alter our standard packaging size or type in the likely event of the standard package size or type not being available at the time of despatch. All orders are accepted subject to force majeure.

SHIPPING AND DELIVERY

For all consignments sold on FOB basis. The risk passes to customer as soon as the goods leave our premises. This is also applicable when delivery is made by our own transport service. If the delivery is postponed for any reason, storage of the goods in our own or third party warehouse shall also be at the customer's risk and responsibility. On intimation to the buyer concerning the readiness of the goods for shipment on FOB basis, the buyer must ensure full insurance cover for any loss or damage. For orders on C&F basis, the buyer must ensure full insurance cover from the time of delivery or despatch from the premises. For consignments on CIF terms, the risk passes to the buyer on arrival at the destination point. Where possible, shipments shall be made as per specified method of the buyer. However, the sellers reserve the right to change the same depending on existing regulations. A special charge shall be levied to meet customized demand regarding special packaging and method of despatch. While the sellers endeavor to supply goods within specified schedules, the seller cannot guarantee a fixed time of delivery. If delay in delivery is caused by circumstances beyond the control of the seller, the time for delivery shall be extended by a reasonable period except where it becomes impossible to supply the goods.

PRODUCT QUALITY AND PACKING

All products are analysed in seller's QC Laboratory. The purity of seller's products is defined in certificates of guarantee, analyse and specifications, which are printed on product labels. Certificate of Guarantee, analysis and specifications shall be provided by the seller on specific request of customer. Such certificates shall be provided free of cost. Purity definitions and typical specifications of all products can be supplied on request. Specifications are subject to change and minor variations from any value listed therein should not cause a dispute. While every effort and utmost care is taken to meet the requirements of quality and exact specification and to ensure that all data are correct. Seller cannot assume any responsibility for their accuracy. Our packing is done under stringent quality control measures and strict adherence to label specifications.

COMPLAINTS AND WARRANTY

All chemicals listed in the price list are for laboratory use only. The seller assumes no responsible in respect of the usage of our products in medicinal, pharmaceutical, agricultural, food, household or cosmetic applications unless specifically agreed by us prior to delivery. The seller has no liability and is not responsible for any loss or damage whatsoever arising out of use and or handling of its products.

All complaints concerning quantity and wrong deliveries must be made to seller within 14 days from the date of receipt of the goods. Failure to notify within the specified period shall be constructed as acceptance of the goods. The seller shall replace all goods and or refund the purchase price of such goods which are proved to be wrongly supplied. Claims concerning breakage should be notified to the transport/insurance company.

PAYMENT CONDITION

For all purchases payments are to be made in advance for 100% invoice value or made through a confirmed, irrevocable letter of credit opened in seller's favour by any prime bank. Letter of credit to be payable at sight at the counters of Seller's Bank, Syndicate Bank, Shoolay Branch, Residency Road, Bangalore-560 025. INDIA.

ARBITRATION

All disputes and differences which may arise out of contractual commitments shall be settled in accordance with the Indian abritration and conciliation act, 1996, by a sole arbitrator agreed between the parties. The venue of the arbitration shall be at Bangalore, India. Courts at Bangalore, India alone shall have jurisdiction over the arbitration proceedings.

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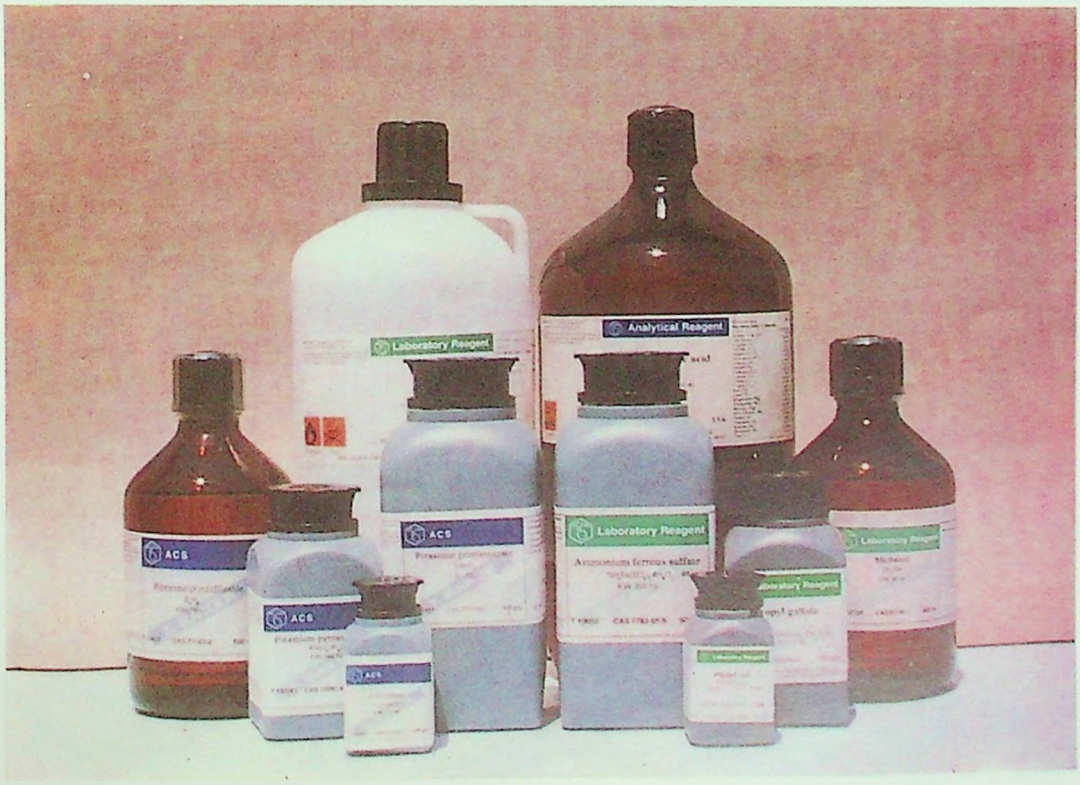
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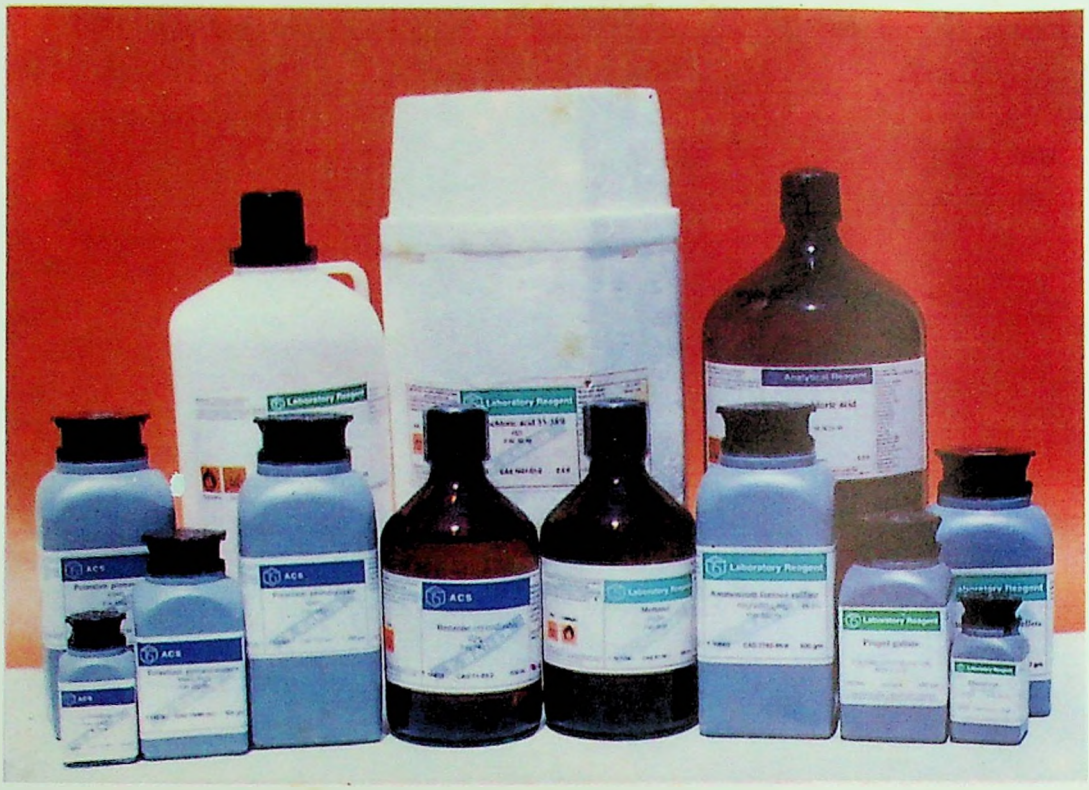
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Laboratory Reagent


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Laboratory Reagent

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 0003 Acacia (Gum arabic) Lab - Grade

CAS 9000-01-5

500	gm	4.10

T 0137 Acetaldehyde Lab - Grade

CAS 75-07-0
CH_3CHO
UN -1089 IMDG - 3.1/I

F.W. 44.05

Acidity (CH_3COOH)	0.15%

500	ml	3.85
6x500	ml	23.10

T 0162 Acetamide Lab - Grade

CAS 60-35-5

CH_3CONH_2	99%	F.W.59.07
Melting Range		79°-81°C
Solubility in Benzene		Passes test
Maximum Limits		
Chloride (Cl)		0.002%
Heavy metal (as Pb)		0.001%
Residue after ignition		0.02%
Iron (Fe)		0.002%
Water (H_2O)		0.3%

500	gm	5.10
6x500	gm	

T 0592 Acetanilide for synthesis Lab - Grade

CAS 103-84-4

$C_6H_5NHCOCH_3$	99%	F.W.135.16
Melting point		115°±2°C

500	gm	7.00

T 0701 Acetic Acid Glacial Lab - Grade

CAS 64-19-7
CH_3COOH
UN - 2789 IMDG - 8/II

F.W. 60.05

Assay (acicimetric)	min. 99.5%
E.P.	min. 15.8 deg C
B.P.	117-119 deg C
Formic Acid	0.1%

500	ml	2.10
1	lt	4.05
2.5	lt	9.60

T 0706 Acetic acid glacial ACS/AR

CAS 64-19-7
UN - 2789 IMDG - 8/II

$C_2H_4O_2$	99.7%	F.W.60.05
Dilution Test		Passes test
Maximum Limits		
Color (APHA)		10
Residue after Evaporation		0.001%
Acetic anhydride [$(CH_3CO)_2O$]		0.01%
Chloride (Cl)		1 ppm
Sulfate (SO_4)		1 ppm
Heavy metals (as Pb)		0.5 ppm
Iron (Fe)		0.2 ppm
Substances Reducing Dichromate		Passes test
Substances Reducing permanganate		Passes test
Titrable Base		0.0004 meq/g

500	ml	2.60
6x500	ml	13.00
1	lt	5.00
2.5	lt	11.00

T 0715 Acetic acid glacial HPLC

CAS 64-19-7 99.8%
UN-2789 IMDG - 8/II
CH_3COOH F.W.60.05

500	ml	6.10
1	lt	11.40

T 0800 Aceto Carmine solution

125	ml	14.00
4x125	ml	42.00

T 0877 Acetone Lab - Grade

CAS 67-64-1
UN 1090 IMDG - 3.1/II

CH_3COCH_3	99.0%	F.W.58.08

500	ml	2.05
6x500	ml	10.25
1	lt	4.10
6x1	lt	20.50
2.5	lt	9.90

T 0882 Acetone ACS/AR

CAS 67-64-1

CH_3COCH_3	99.5%	F.W.58.08
UN - 1090 IMDG - 3.1/II		
Solubility in water		Passes test
Maximum Limits		
Color (APHA)		10
Residue after Evaporation		0.001%
Titrable Acid		0.0003 meq/g
Titrable Base		0.0006 meq/g
Aldehyde (as HCHO)		0.002%
Isopropyl alcohol		0.05%
Methanol		0.05%
Substances Reducing Permanganate		Passes test
Water		0.5%

500	ml	2.40
6x500	ml	12.00
1	lt	4.45
6x1	lt	22.25
2.5	lt	10.90

T 0979 Acetonitrile Lab - Grade

CAS 75-05-8
CH_3CN
UN - 1648, IMDG - 3.2/II

F.W.41.05

B.P.	80-82 deg C
Assay (GC)	min. 99.0%
H_2	0.2%
pH (10% soln)	Neutral to litmus.

500	ml	3.85
2.5	lt	17.40

T 0984 Acetonitrile ACS/AR

CAS 75-05-8
UN-1648 IMDG - 3.2 /II

CH_3CN	99.5%	F.W.41.05
Appearance		Clear
Maximum Limits		
Color (APHA)		10
Residue after Evaporation		0.005%
Titrable Acid		8 µeq/g
Titrable Base		0.6 µeq/g
Water		0.3%

500	ml	6.85
6x500	ml	34.25
2.5	lt	31.40

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS.

T 0983 Acetophenone Lab-Grade

CAS 98-86-2

$C_6H_5COCH_3$	99.0%	F.W.120.15
Freezing Point		19°-20°C
Maximum Limit		
Residue after Evaporation		0.01%

250	ml	3.50
6x250	ml	17.50
500	ml	6.25

T 3601 Acridine Orange Lab-Grade

CAS 10127-02-3
C.I. NO. 46005

	F.W.369.94
DYE CONTENT	~90%

5	gm	3.75
10	gm	6.85

T 13981 Balsam Canada -Neutral Clear solution

CAS - 8007-47-4
Light yellowish brown viscous transparent liquid.
Refractive index at 25 deg C 1.52 -1.54

30	ml	1.70
100	ml	4.20

T 3620 Acrylic Acid Lab-Grade

CAS 79-10-7
$C_3H_4O_2$
UN - 2218, IMDG - 8/II

	F.W. 72.06
Assay (GC)	Min. 99.0%
H_2O	<0.2%

500	ml	8.90

T 3800 Albert's Stain 'A' solution

125	ml	1.30
4x125	ml	3.90

T 3805 Albert's Stain 'B' solution

125	ml	1.30
4x125	ml	3.90

T 3810 Alkaline Copper Solution (folin & Wu)

125	ml	0.45
4x125	ml	1.35

T 4440 Alizarin for microscopy pH indicator Lab-Grade

CAS 72-48-0 [C.I.58000]
$C_{14}H_8O_4$ F.W.240.20
Visual Transition intervals pH 5.5 to pH 6.3 (Yellow to red)
pH 10.1 to ph 12.1 (red to purple)
Melting point 287°-289°C

25	gm	2.85
100	gm	8.85

T 5315 Aluminum ammonium sulfate Lab-Grade

CAS 7784-26-1

$AlNH_4(SO_4)_2$	99.0%	F.W.453.33

500	gm	1.85

T 5320 Aluminium ammonium sulfate ACS/AR

CAS 7784-26-1

$AlNH_4(SO_4)_2.12H_2O$	98.0-102.0%	F.W.453.33
Maximum Limits		
Insoluble matter		0.005%
Chloride (Cl)		0.001%
Calcium (Ca)		0.05%
Heavy metals (as Pb)		0.001%
Iron (Fe)	0.001%	
Potassium (K)		0.05%
Sodium (Na)		0.01%

500	gm	2.70
6x500	gm	13.50

T 5461 Aluminium chloride anhydrous Lab-Grade

CAS 7446-70-0
UN - 1726 IMDG - 8/II

$AlCl_3$	99.0%	F.W.133.34
Maximum Limits		
Heavy metals (as Pb)		0.005%
Iron (Fe)	0.01%	
Substances not Pptd. by NH_4OH		0.5%

500	gm	2.70
6x500	gm	13.70

T 5468 Aluminium chloride hydrated Lab -Grade

CAS 7784-13-6
UN-1726 IMDG - 8/II

$AlCl_3.6H_2O$	97.0%	F.W.241.43
Maximum Limits		
Heavy metals (as Pb)		0.0005%
Arsenic (As)		0.0005%
Insoluble matter		0.01%
Iron (Fe)		0.005%
Substances not Pptd. by NH_4OH		0.2%
Sulfate (SO_4)		0.02%

500	gm	6.00
6x500	gm	30.00

T 5473 Aluminium chloride hydrated ACS/AR

CAS 7784-13-6
UN - 1726 IMDG - 8/II

$AlCl_3.6H_2O$	99.5%	F.W.241.43
Maximum Limits		
Ammonia		0.002%
Acidity (HCl)		0.1%

500	gm	10.00
6x500	gm	50.00

T 5821 Aluminium Oxide Active Neutral Lab-Grade

CAS 1344-28-1
Al_2O_3

	F.W. 101.96
Chloride	0.1%

500	gm	4.20

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 5809 Aluminium potassium sulfate Lab-Grade

CAS 7784-24-9

$AlK(SO_4)_2.12H_2O$	99.5-100.50%	F.W.474.39
Maximum Limits		
Ammonium salts		Passes test
Fluoride		0.003%
Heavy metals (as Pb)		0.001%
Selenium		0.003%

500	gm	1.25
6x500	gm	6.25

T 5814 Aluminium potassium sulfate ACS/AR

CAS 7784-24-9

$AlK(SO_4)_2.12H_2O$	99.0%	F.W.474.39
Maximum Limits		
Insoluble matter		0.005%
Chloride (Cl)		5 ppm
Ammonium (NH_4)		0.005%
Heavy metals (as Pb)		0.001%
Iron (Fe)		0.001%
Sodium (Na)		0.02%

500	gm	6.00
6x500	gm	30.00

T 5990 Aluminium sulfate Lab-Grade

CAS 7784-31-8

$Al_2(SO_4)_3.(14\text{-}18)H_2O$	98.0%

500	gm	1.75

T 5995 Aluminium sulfate ACS/AR

CAS 7784-31-8

$Al_2(SO_4)_3.(14\text{-}18)H_2O$	98.0-102.0%
Maximum Limits	
Insoluble matter	0.01%
Chloride (Cl)	0.005%
Substances not Pptd. by Ammonium hydroxide (as SO_4)	0.2%
Heavy metals (as Pb)	0.001%
Iron (Fe)	0.002%

500	gm	2.55

T 6232 Amido black 10 B Lab-Grade

CAS 1064-48-8	[C.I.20470]
$C_{22}H_{14}N_6O_9S_2Na_2$	F.W.616.50
Absorption Max. (in water)	618 nm

100	gm	5.40

T 9914 Ammonia solution sp.gr 0.910 Lab-Grade (Ammonium hydroxide)

CAS 1336-21-6

UN-3318 IMDG - 2.3

NH_3	27-30%	F.W.35.05
Maximum Limits		
Heavy metals (as Pb)		0.0005%
Nonvolatile residue		0.02%
Readily oxidizable substances		Passes test

500	ml	1.35
6x500	ml	6.75
1	lt	2.40
2.5	lt	5.25
4x2.5	lt	18.25
5	lt	9.20

T 9919 Ammonia solution sp.gr 0.910 ACS/AR (Ammonium hydroxide)

CAS 1336-21-6

UN - 3318 IMDG - 2.3

NH_3	28.0-30.0%	F.W.35.05
Appearance		Passes test
Maximum Limts		
Residue after Ignition		0.002%
Carbon dioxide (CH_2)		0.002%
Chloride (Cl)		0.5 ppm
Phosphate (PO_4)		2 ppm
Total sulfur (as SO_4)		2 ppm
Heavy metals (as Pb)		0.5 ppm
Iron (Fe)		0.2 ppm
Substances Reducing Permanganate		Passes test

500	ml	1.60
6x500	ml	8.00
1	lt	3.00
2.5	lt	6.25
5	lt	10.90

T 9992 Ammonium bromide Lab-Grade

CAS 12124-97-9

NH_4Br	99.0%	F.W.97.94
pH of a 5% solution @ 25°C		4.5-6.0
Maximum Limits		
Insoluble matter		0.005%
Residue after Ignition		0.01%
Bromate (BrO_3)		Passes test (limit about 0.002%)
Iodide (I)		Passes test (limit about 0.005%)
Sulfate (SO_4)		0.005%
Barium (Ba)		0.002%
Heavy metals (as Pb)		0.0005%
Iron (Fe)		0.0005%

500	gm	6.85
6x500	gm	34.25

T 10071 Ammonium carbonate Lab-Grade

CAS 506-87-6;

Consists of approximately equimolecular proportions of

$(NH_4)_2CO_3$	30-34%

500	gm	2.50

T 10076 Ammonium carbonate ACS/AR

CAS 506-87-6;

$(NH_4)_2CO_3$	30.0%
Maximum Limits	
Insoluble matter	0.005%
Nonvolatile matter	0.01%
Chloride (Cl)	5 ppm
Sulfur compounds (as SO_4)	0.002%
Heavy metals (as Pb)	5 ppm
Iron (Fe)	5 ppm

500	gm	5.70
6x500	gm	28.50

T 10093 Ammonium ceric nitrate Lab-Grade

CAS 16774-21-3

$(NH_4)_2[Ce(NO_3)_6]$	98.0%	F.W.548.23

100	gm	7.40

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 10098 Ammonium ceric nitrate ACS/AR

CAS 16774-21-3
$(NH_4)_2[Ce(NO_3)_6]$ 99.0% F.W.548.23

100	gm	8.55

T 10110 Ammonium ceric sulfate Lab-Grade

CAS 10378-47-9
$(NH_4)_4[Ce(SO_4)_4].2H_2O$ 98.0% F.W.632.53

100	gm	5.90

T 10115 Ammonium ceric sulfate ACS/AR

CAS 10378-47-9
$(NH_4)_4[Ce(SO_4)_4].2H_2O$ 99.0% F.W.632.53

100	gm	8.25

T 10130 Ammonium chloride Lab-Grade

CAS 12125-02-9
NH_4Cl 99% F.W.53.49

500	gm	1.55
6x500	gm	7.75
5	kg	13.40

T 10135 Ammonium chloride ACS/AR

CAS 12125-02-9
NH_4Cl 99.5% F.W.53.49

pH of a 5% solution @ 25°C	4.5-5.5
Maximum Limits	
Insoluble matter	0.005%
Residue after ignition	0.01%
Phosphate (PO_4)	2 ppm
Sulfate (SO_4)	0.002%
Calcium and Magnesium Ppt.	0.002%
Heavy metals (as Pb)	5 ppm
Iron (Fe)	2 ppm

500	gm	3.25

T 10316 tri-Ammonium citrate Lab-Grade

CAS 3458-72-8
$(NH_4)_3C_6H_5O_7$ 97-103% F.W.243.22

500	gm	7.85

T 10321 tri-Ammonium citrate ACS/AR

CAS 3458-72-8
$(NH_4)_3C_6H_5O_7$ F.W.243.22

Assay	98.5-101.00%
Chloride	0.001%
Oxalate	0.01%

500	gm	9.25
6x500	gm	46.25

T 10460 Ammonium dichromate Lab-Grade

CAS 7789-09-5
UN-1439 IMDG - 5.I/II
$(NH_4)_2Cr_2O_7$ 97% F.W.252.07

500	gm	5.25

T 10465 Ammonium dichromate ACS/AR

CAS 7789-09-5
UN-1439 IMDG - 5.I/II
$(NH_4)_2Cr_2O_7$ 99.5% F.W.252.07

Maximum Limits	
Insoluble matter and ammonium hydroxide Pptd.	0.005%
Loss on drying at 105°C	3.0%
Chloride (Cl)	0.005%
Sulfate (SO_4)	0.01%
Calcium (Ca)	0.002%
Iron (Fe)	0.002%
Sodium (Na)	0.005%

500	gm	13.75

T 10481 Ammonium dihydrogen orthophosphate Lab-Grade

CAS 7722-76-1
$NH_4H_2PO_4$ 98-101% F.W.115.03

500	gm	3.70

T 10486 Ammonium dihydrogen orthophosphate ACS/AR

CAS 7722-76-1
$NH_4H_2PO_4$ 98.0% F.W.115.03

pH of a 5% solution @ 25°C	3.8-4.4
Maximum Limits	
Insoluble matter	0.005%
Ammonium hydroxide Ppt.	0.005%
Chloride (Cl)	5 ppm
Nitrate (NO_3)	0.001%
Sulfur compounds (as SO_4)	0.005%
Heavy metals (as Pb)	5 ppm
Iron (Fe)	0.001%
Potassium (K)	0.005%
Sodium (Na)	0.005%

500	gm	4.70
6x500	gm	23.50

T 10603 Ammonium ferric sulfate Lab-Grade

CAS 7783-83-7
$NH_4Fe(SO_4)_2.12H_2O$ 98-101% F.W.482.18

500	gm	3.00

T 10608 Ammonium ferric sulfate ACS/AR

CAS 7783-83-7
$NH_4Fe(SO_4)_2.12H_2O$ 98.5-102.0% F.W.482.20

Appearance	Pale violet crystals
Maximum Limits	
Insoluble matter	0.01%
Chloride (Cl)	0.001%
Nitrate (NO_3)	0.01%
Copper (Cu)	0.003%
Ferrous iron (Fe^{+2})	Passes test (limit about 0.001%)
Substances not Pptd. by Ammonium hydroxide	0.05%
Zinc (Zn)	0.003%

500	gm	3.55
6x500	gm	17.75

T 10660 Ammonium ferrous sulfate Lab-Grade

CAS 7783-85-9
$(NH_4)_2Fe(SO_4)_2.6H_2O$ 98.5% F.W.392.13

500	gm	1.85

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 10665 Ammonium ferrous sulfate ACS/AR

CAS 7783-85-9
$(NH_4)_2Fe(SO_4)_2.6H_2O$ 98.5% F.W.392.13

Maximum Limits

Insoluble matter	0.01%
Phosphate (PO_4)	0.003%
Copper (Cu)	0.003%
Ferric iron (Fe^{3+})	0.01%
Manganese (Mn)	0.01%
Substances not Pptd. by Ammonium hydroxide	0.05%
Zinc (Zn)	0.003%

500	gm	4.00
6x500	gm	20.00

T 10672 Ammonium fluoride Lab-Grade

CAS 12125-01-8
UN-2505 IMDG - 6.1/III
NH_4F 95% F.W.37.04

500	gm	6.50

T 10677 Ammonium fluoride ACS/AR

CAS 12125-01-8
UN-2505 IMDG - 6.1/III
NH_4F 98.0% F.W.37.04

Maximum Limits

Insoluble matter	0.005%
Residue after ignition	0.01%
Chloride (Cl)	0.001%
Sulfate (SO_4)	0.005%
Heavy metals (as Pb)	5 ppm
Iron (Fe)	5 ppm

250	gm	41.00

T 10800 Ammonium hydrogen carbonate Lab-Grade (Ammonium bicarbonate)

CAS 1066-33-7
NH_4HCO_3 98.5% F.W.79.06

500	gm	2.00

T 10805 Ammonium hydrogen carbonate ACS/AR (Ammonium bicarbonate)

CAS 1066-33-7
NH_4HCO_3 99.0% F.W.79.06
pH of a 5% solution @ 25°C 7.0-7.8

Maximum Limits

Chloride (Cl)	0.0005%
Heavy metals (as Pb)	0.001%
Insoluble matter	0.005%
Iron (Fe)	0.0005%
Residue after ignition	0.01%
Sulfate (SO_4)	0.001%

500	gm	6.10
6x500	gm	30.50

T 11221 Ammonium molybdate ACS/AR

CAS 12054-85-2
$(NH_4)_6Mo_7O_{24}.4H_2O$ 81-83% F.W.1235.86

Maximum Limits

Insoluble matter	0.005%
Chloride (Cl)	0.002%
Nitrate (NO_3)	Passes test (limit about 0.003%)
Arsenate, Phosphate and Silicate (as SiO_2)	0.001%
Phosphate (PO_4)	5 ppm
Sulfate (SO_4)	0.02%
Heavy metals (as Pb)	0.001%
Magnesium and other Alkaline earths	0.02%

100	gm	4.25
6x100	gm	21.25
500	gm	20.00
6x500	gm	100.00

T 11327 Ammonium nitrate Lab-Grade

CAS 6484-52-2
UN 1942 IMDG - 5.1/III
NH_4NO_3 98.0% F.W.80.04

500	gm	1.85

T 11332 Ammonium nitrate ACS/AR

CAS 6484-52-2
UN-1942 IMDG- 5.1/III
NH_4NO_3 98% F.W.80.04
pH of a 5% solution @ 25°C 4.5-6.0

Maximum Limits

Insoluble matter	0.005%
Residue after ignition	0.01%
Chloride (Cl)	5 ppm
Nitrite (NO_2)	Passes test (limit about 5 ppm)
Phosphate (PO_4)	5 ppm
Sulfate (SO_4)	0.002%
Heavy metals (as Pb)	5 ppm
Iron (Fe)	2 ppm

500	gm	3.70
6x500	gm	

T 11381 Ammonium oxalate Lab-Grade

CAS 6009-70-7
$(NH_4)_2C_2O_4.H_2O$ 99.0% F.W.142.11

500	gm	2.70

T 11386 Ammonium oxalate ACS/AR

CAS 6009-70-7
$(NH_4)_2C_2O_4.H_2O$ 99.0-101.0% F.W.142.11

Maximum Limits

Insoluble matter	0.005%
Residue after ignition	0.02%
Chloride (Cl)	0.002%
Sulfate (SO_4)	0.002%
Heavy metals (as Pb)	5 ppm
Iron (Fe)	2 ppm

500	gm	3.85
6x500	gm	19.25

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 11409 Ammonium persulfate Lab-Grade

CAS 7727-54-0
UN - 1444 IMDG - 5.1/III
$(NH_4)_2S_2O_8$ 98.0% F.W.228.19

500	gm	3.40

T 11414 Ammonium persulfate ACS/AR

CAS 7727-54-0
UN - 1444 IMDG - 5.1/III
$(NH_4)_2S_2O_8$ 98.5% F.W.228.19

Maximum Limits	
Insoluble matter	0.005%
Residue after ignition	0.05%
Titrable free acid	0.04 meq/g
Chloride and Chlorate (as Cl)	0.001%
Heavy metals (as Pb)	0.005%
Iron (Fe)	0.001%
Manganese (Mn)	0.5 ppm

500	gm	4.25
6x500	gm	21.25

T 11640 Ammonium sulfate Lab-Grade

CAS 7783-20-2
$(NH_4)_2SO_4$ 99% F.W.132.12

500	gm	1.30

T 11645 Ammonium sulfate ACS/AR

CAS 7783-20-2
$(NH_4)_2SO_4$ 99% F.W.132.12

pH of a 5% solution @ 25°C	5.0-6.0
Maximum Limits	
Insoluble matter	0.005%
Residue after ignition	0.005%
Chloride (Cl)	5 ppm
Nitrate (NO_4)	0.001%
Phosphate (PO_4)	5 ppm
Heavy metals (as Pb)	5 ppm
Iron (Fe)	5 ppm

500	gm	3.25
6x500	gm	16.25
5	kg	29.25

T 11687 Ammonium (+) tartrate Lab-Grade

CAS 3164-29-2
$[CH(OH)COONH_4]_2$ 98% F.W.184.15

500	gm	25.70

T 11692 Ammonium (+) tartrate ACS/AR

CAS 3164-29-2
$[CH(OH)COONH_4]_2$ 99.0% F.W.184.15

Maximum Limits	
Calcium (Ca)	0.02%
Chloride (Cl)	0.005%
Heavy metals (as Pb)	0.001%
Iron (Fe)	0.001%
Residue after Ignition	0.01%
Sulfate (SO_4)	0.002%

500	gm	27.50

T 11751 Ammonium thiocyanate Lab-Grade

CAS 1762-95-4
NH_4SCN 98% F.W.76.12
Melting point 149°C

500	gm	4.20

T 11756 Ammonium thiocyanate ACS/AR

CAS 1762-95-4
NH_4SCN 99% F.W.76.12

Appearance	Colorless or white crystals
pH of a 5% solution @ 25°C	4.5-6.0
Maximum Limits	
Insoluble matter	0.005%
Residue after ignition	0.025%
Chloride (Cl)	0.005%
Sulfate (SO_4)	0.005%
Heavy metals (as Pb)	5 ppm
Iron (Fe)	3 ppm
Iodine-Consuming substance	0.004 meq/g

500	gm	5.55
6x500	gm	27.75

T 12567 Aniline Lab-Grade

CAS 62-53-3
UN-1547 IMDG 6.1/II
$C_6H_5NH_2$ 99% F.W.93.13

500	ml	4.10

T 12572 Aniline ACS/AR

CAS 62-53-3
UN - 1547 IMDG 6.1/II
$C_6H_5NH_2$ 99.5% F.W.93.13

Maximum Limits	
Color (APHA)	250
Residue after ignition	0.005%
Chlorobenzene (C_6H_5Cl)	0.01%
Hydrocarbons	Passes test
Nitrobenzene ($C_6H_5NO_2$)	Passes test (limit about 0.001%)

500	ml	6.85
6x500	ml	34.25

T 12590 Aniline Blue (spirit soluble) Lab-Grade

C.I. 42775
CAS 8004-91-9
Abs.max (Methanol) 591 nm

25	gm	4.00
100	gm	12.00

T 12593 Aniline blue (water soluble) Lab-Grade

[C.I.42755]
CAS 28631-66-5
$C_{32}H_{25}N_3O_9S_3Na_2$ F.W.737.74

Dye Content (Titanometry)	> 25%
Abs.max (water + 5 ml 0.1 N HCl)	594-610

25	gm	2.00
100	gm	6.00

T. BAKER LAB CHEMICALS

T 12602 Aniline hydrochloride Lab-Grade

CAS 142-04-1
$C_6H_5NH_2.HCl$
UN - 1548 IMDG - 6.1/III

F.W.129.59

Assay	99-100.5%
M.P.	198-200 deg C

250	gm	6.25

T 12672 Aniline sulfate Lab-Grade

CAS 542-16-5
$(C_6H_5NH_2)_2H_2SO_4$

F.W.284.33

Assay (acidimetric)	Min 99.0%
Chloride	.002%

250	gm	8.85

T 13041 Anthranilic acid ACS/AR

CAS 118-92-3
$NH_2C_6H_4COOH$ 98% F.W.137.13
Melting range within 1°C including 147°C

25	gm	4.30

T 13061 Anthraquinone Lab-Grade

CAS 84-65-1
$(C_6H_4CO)_2$ 98% F.W.208.22

500	gm	9.10

T 13175 Antimony (metal) lumps Lab-Grade

CAS 7440-36-0
Sb 99% F.W. 121.75

100	gm	3.40
500	gm	13.75

T 13309 Antimony potassium (+) tartrate Lab-Grade

CAS 28300-74-5
UN - 1551 IMDG - 6.1/III
$K(SbO)C_4H_4O_6$ 99.0-103.0% F.W.667.87

250	gm	7.70
500	gm	31.00

T 13314 Antimony potassium (+) tartrate ACS/AR

CAS 28300-74-5
UN -1551 IMDG - 6.1/III
$K(SbO)C_4H_4O_6$ 99.0% F.W.324.92
Maximum Limits

Titrable acid or base	0.020 meq/g
Loss on drying	2.7%
Arsenic (As)	0.015%

100	gm	4.40
500	gm	18.50
6x500	gm	92.50

T 13383 Antimony trichloride Lab-Grade

CAS 10025-91-9
UN -1733 IMDG - 8/II
$SbCl_3$ 98.5% F.W.228.12

500	gm	14.10
6x500	gm	70.50

T 13388 Antimony trichloride ACS/AR

CAS 10025-91-9
UN - 1733 IMDG - 8/II
$SbCl_3$ 99.0% F.W.228.12
Maximum Limits

Insoluble in chloroform	0.05%
Sulfate (SO_4)	0.005%
Arsenic (As)	0.02%
Copper (Cu)	0.001%
Iron (Fe)	0.002%
Lead (Pb)	0.005%
Substances not Pptd. by hydrogen sulfide (as Sufate)	0.1%

500	gm	18.40
6x500	gm	92.0

T 13413 Antimony trioxide Lab Grade

CAS 1309-64-4
Sb_2O_3 99.0% F.W.291.52
Maximum Limits

Arsenic (As)	0.1%
Chloride (Cl)	0.005%
Iron (Fe)	0.002%

500	gm	11.00
6x500	gm	55.00

T 13923 Arsenic Trioxide Lab-Grade

AS_2O_3
CAS 1327-53-3
UN - 1561 IMDG - 6.1/II

F.W. 197.84

Assay (iodometric)	min. 95%
Iron	0.05%

500	gm	2.85

T 15278 Barium carbonate Lab-Grade

CAS 513-77-9
UN-1564 IMDG - 6.1/ II
$BaCO_3$ 99-101% F.W.197.34

500	gm	6.10
6x500	gm	30.50

T 15283 Barium carbonate ACS/AR

CAS 513-77-9
UN-1564 IMDG - 6.1/II
$BaCO_3$ 99.0-101.0% F.W.197.34
Maximum Limits

Insoluble in dilute hydrochloric acid	0.015%
Chloride (Cl)	0.002%
Water soluble titrable base	0.002 meq/g
Oxidizing substances (as NO_3)	0.005%
Sulfide (S)	0.001%
Substances not Pptd. by sulfuric acid	0.25%
Calcium (Ca)	0.05%
Heavy metals (as Pb)	0.001%
Iron (Fe) 0.002%	
Strontium (Sr)	0.7%

500	gm	20.50
6x500	gm	102.50

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 15287 Barium chloride extra pure Lab-Grade

CAS 10326-27-9

$BaCl_2.2H_2O$	99-102%	F.W.244.26
500 gm		2.15
6x500 gm		10.75

T 15292 Barium chloride ACS /AR

CAS 10326-27-9

$BaCl_2.2H_2O$	99.0%	F.W.244.26
Loss on drying @ 150°C		14.0-16.0%
pH of a 5% solution @ 25°C		5.2-8.2
Maximum Limits		
Insoluble matter		0.005%
Oxidizing substances (as NO_3)		0.005%
Substances not Pptd. by sulfuric acid		0.05%
Calcium (Ca)		0.05%
Heavy metals (as Pb)		5 ppm
Iron (Fe)		2 ppm
Strontium (Sr)		0.1%
500 gm		4.10
6x500 gm		20.50

T 15300 Barium chromate Lab-Grade

CAS 10294-40-3

$BaCrO_4$	F.W.253.37
500 gm	15.60

T 15305 Barium chromate ACS/AR

CAS 10294-40-3

$BaCrO_4$	F.W.253.37
100 gm	12.25

T 15447 Barium diphenylamine sulfonate Lab-Grade

CAS 6211-24-1

$C_{24}H_{20}BaN_2O_6S_4$	F.W.633.9
5 gm	3.00
25 gm	12.00

T 15500 Barium hydroxide Lab-Grade

CAS 12230-71-6

$Ba(OH)_2.8H_2O$	97%	F.W.315.47
500 gm		2.25
6x500 gm		11.25

T 15789 Barium nitrate Lab-Grade

CAS 10022-31-8
UN-1446 IMDG - 5.1/II

$Ba(NO_3)_2$	99%	F.W.261.34
500 gm		2.10

T 15794 Barium nitrate ACS/AR

CAS 10022-31-8
UN - 1446 IMDG - 5.1/II

$Ba(NO_3)_2$	99.5%	F.W.261.34
pH of a 5% solution @ 25°C		5.0-8.0
Maximum Limits		
Insoluble matter		0.01%
Chloride (Cl)		5 ppm
Substances not Pptd. by sulfuric acid		0.05%
Calcium (Ca)		0.05%
Heavy metals (as Pb)		5 ppm
Iron (Fe)		2 ppm
Strontium (Sr)		0.1%
500 gm		4.00

T 15845 Barium oxide Lab-Grade

CAS 1304-28-5
UN - 1884 IMDG 6.1/III

BaO	95%	F.W.153.33
100 gm		8.50

T 15896 Barium peroxide Lab-Grade

CAS 1304-29-6

BaO_2	88%	F.W.169.34
Maximum Limits		
Chloride (Cl)		0.02%
Heavy metals (as Pb)		0.002%
Insoluble in HCl		1.0%
Iron (Fe)		0.05%
Substances not Pptd. by Sulfuric acid		1.0%
500 gm		7.50

T 16089 Benedict's Reagent (Qualitative) Lab-Grade

Sensitivity test:

0.5% Glucose	- bluish green
1.0% Glucose	- yellow
1.5% Glucose	- brownish yellow
>2.0% Glucose	- brick-red colour
500 ml	1.35

T 16190 Benzaldehyde Lab-Grade

CAS 100-52-7
UN - 1990 IMDG - 9/III

C_6H_5CHO	98.5%	F.W.106.12
500 ml		6.40
6x500 ml		32.00

T 16195 Benzaldehyde ACS/AR

CAS 100-52-7
UN - 1990 IMDG - 9/III

C_6H_5CHO	99%	F.W.106.12
Maximum Limits		
Chlorinated compounds (as Cl)		Passes test
Hydrochloride acid		Passes test
Nitrobenzene		Passes test
Solubility		Passes test
500 ml		10.25

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 16344 Benzanilide Lab-Grade

CAS 93-98-1
$C_6H_5CONHC_6H_5$ 99% F.W.197.24

100	gm	3.85
500	gm	15.40

T 16398 Benzene crystallizable Lab-Grade

CAS 71-43-2
C_6H_6
UN - 1114 IMDG - 3.2/II
Maximum Limits

Color (APHA)	10
Residue after evaporation	0.001%
Substances darkened by sulfuric acid	Passes test
Thiophene	Passes test (limit about 1 ppm)
Sulfur compounds (as S)	0.005%
Water (H_2O)	0.005%

500	ml	1.60
2.5	lt	6.55

T 16403 Benzene crystallizable ACS/AR

CAS 71-43-2
UN - 1114 IMDG - 3.2/II
C_6H_6 99.0% F.W.78.11
Maximum Limits

Color (APHA)	10
Residue after evaporation	0.001%
Substances darkened by sulfuric acid	Passes test
Thiophene	Passes test (limit about 1 ppm)
Sulfur compounds (as S)	0.005%
Water (H_2O)	0.005%

500	ml	1.75
2.5	lt	7.40

T 16422 Benzene thiophene free ACS/AR

CAS 71-43-2
UN-1114 IMDG - 3.2 /II
C_6H_6 99.7% F.W.78.11
Maximum Limits

Color (APHA)	10
Residue after evaporation	0.001%
Substances darkened by sulfuric acid	Passes test
Sulfur compounds (as S)	0.005%
Water (H_2O)	0.005%

500	ml	2.25
6x500	ml	11.25

T 16437 Benzene for spectroscopy

CAS 71-43-2
UN -1114 IMDG - 3.2 /II
C_6H_6 99.8% F.W.78.11
Ultraviolet absorbance (1 cm cell vs. water)

λ(nm)	280	290	300	330	350	380-400
Limit	1.00	0.30	1.10	0.04	0.02	0.01

Maximum Limits

Color (APHA)	10
Residue after evaporation	0.001%
Substances darkened by sulfuric acid	Passes test
Thiophene	Passes test (limit about 1 ppm)
Sulfur compounds (as S)	0.005%
Water (H_2O)	0.05%

500	ml	4.00
6x500	ml	20.00
1	lt	7.70

T 17007 Benzoic acid Lab-Grade

CAS 65-85-0
UN - 2769 IMDG - 6.1/II
$C_7H_6O_2$ 99.5% F.W.122.12

500	gm	3.10
5	kg	28.00

T 17012 Benzoic acid ACS/AR

CAS 65-85-0
UN - 2769 IMDG -6.1/II
$C_7H_6O_2$ 99.9% F.W.122.12
Freezing point 122°-123°C
Maximum Limits

Residue after ignition	0.005%
Insoluble in methanol	0.005%
Chlorine compounds (as Cl)	0.005%
Heavy metals (as Pb)	5 ppm
Substances reducing permanganate	Passes test

500	gm	17.00

T 17068 Benzophenone Lab-grade

CAS 119-61-9
$(C_6H_5)_2CO$ 99.0% F.W.182.22
Melting point within 2°C including 48.5°C ± 0.1°C

500	gm	10.85

T 17403 Benzoyl chloride Lab-Grade

CAS 98-88-4
UN - 1736 IMDG - 8/II
C_6H_5COCl 99% F.W.140.57

500	ml	5.50

T 17408 Benzoyl chloride ACS/AR

CAS 98-88-4
UN-1736 IMDG -8/II
C_6H_5COCl 99.0% F.W.140.57
Freezing point -2.0° to 0.0°C
Maximum Limits

Residue after ignition	0.005%
Phosphorous compounds (as P)	0.002%
Heavy metals (as Pb)	0.001%
Iron (Fe)	0.001%

500	ml	8.80
6x500	ml	

T 17711 Benzyl acetate Lab-Grade

CAS 140-11-4
UN - 1736 IMDG - 8/II
$CH_3CO_2CH_2C_6H_5$ 98.0% F.W.150.18
Chloridated compounds Passes test

500	ml	4.80

T 17739 Benzyl alcohol Lab-Grade

CAS 100-51-6
UN - 1736 IMDG - 8/II
C_7H_8O 99% F.W.108.14

500	ml	4.80
2.5	lt	20.00

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 17744 Benzyl alcohol ACS/AR

CAS 100-51-6
C_7H_8O 99.0% F.W.108.14

Maximum Limits

Color (APHA)	20
Residue after Ignition	0.005%
Acetophenone ($C_6H_5COCH_3$)	0.02%
Benzaldehyde (C_6H_5CHO)	0.01%

500	ml	6.00
2.5	lt	28.00

T 17806 Benzyl benzoate Lab-Grade

CAS 120-51-4
$C_6H_5COOCH_2C_6H_5$ 98% F.W.212.25

500	ml	5.50

T 20305 Bismark Brown Lab-Grade

C.I.NO. 21010
CAS 1051-38-6
$C_{12}H_{14}N_8 2HCl$
F.W.461.40

DYE content	~40%
LOD (110 deg C)	Max. 5%

5	gm	0.30
10	gm	0.50

T 20572 Bismuth (III) nitrate Lab-Grade

CAS 10035-06-0
$Bi(NO_3)_2.5H_2O$ 98% F.W.485.07

100	gm	4.50
500	gm	20.00

T 20867 Bismuth sulfate Lab-Grade

CAS 7787-68-0
$Bi_2(SO_4)_3$ 90% F.W.706.18

250	gm	19.20

T 20875 Biuret Reagent indicator solution

125	ml	1.25
4x125	ml	3.75

T 21030 Boric acid Lab-Grade

CAS 10043-35-3
H_3BO_3 99.5% F.W.61.83

500	gm	2.70
5	kg	22.80

T 21035 Boric acid ACS/AR

CAS 10043-35-3
H_3BO_3 99.5% F.W.61.83

Maximum Limits

Insoluble in methanol	0.005%
Nonvolatile with methanol	0.05%
Chloride (Cl)	0.001%
Phosphate (PO_4)	0.001%
Sulfate (SO_4)	0.01%
Calcium (Ca)	0.005%
Heavy metals (as Pb)	0.001%
Iron (Fe)	0.001%

500	gm	8.10
6x500	gm	40.50

T 21000 Borax Carmine (Grenacher) alcoholic staining solution

125	ml	3.40
4x125	ml	10.20

T 21005 Borax Carmine (Grenacher) aqueous staining solution

125	ml	2.00
4x125	ml	6.00

T 21010 Brilliant Cresyl Blue indicator solution

125	ml	3.10
4x125	ml	9.90

T 20901 Brilliant Green Indicator Lab-Grade

(C.I. No. 42040) absorption max.....628-632 nm

5	gm	0.60
10	gm	0.90

T 20906 Brilliant Green 1% Aqueous solution

125	ml	1.70
4x125	ml	5.10

T 20951 Brilliant Yellow Lab-Grade

(C.I. NO. 24890)
pH 6.4-9.4 yellow-orange -red

5	gm	1.50
10	gm	2.30

T 21487 Bromine Lab-Grade

CAS 7726-95-6
UN - 1744 IMDG - 8/I
Br_2 99.0% F.W.159.82

5x20	ml	6.60
250	ml	10.80

T 21492 Bromine ACS/AR

CAS 7726-95-6
UN-1744 IMDG-8/I
Br_2 99.5% F.W.159.82

Maximum Limits

Residue after evaporation	0.005%
Chloride (Cl)	0.05%
Iodine (I)	0.001%
Organic bromine compounds	Passes test
Sulfur compounds (as S)	0.001%
Heavy metals (as Pb)	2 ppm
Nickel (Ni)	5 ppm

250	ml	14.00

T 21807 Bromobenzene Lab-Grade

CAS 108-86-1
UN-2514 IMDG -3.3/III
C_6H_5Br 98.0% F.W.157.01

250	ml	6.80

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 21851 Bromocresol Green Lab-Grade

CAS 76-60-8

F.W. 698.04

$C_{21}H_{14}Br_4O_5S$

pH transition range:

pH 3.8 to 5.4	yellowish green to blue
Abs.max pH 3.8	438-443 nm
pH 5.4	615-618 nm
LOD (110 deg C)	3%

1	gm	1.90
5	gm	7.50

T 21856 Bromocresol Green indicator solution standard

pH transition range:

pH 3.8 to 5.4 — yellowish green to blue

125	ml	1.05
4x125	ml	3.15

T 21861 Bromocresol purple Lab-Grade

CAS 115-40-2

F.W. 540.24

$C_{21}H_{10}Br_2S$

pH transition range:

pH 5.2 - 6.8	greenish yellow - blue violet
Abs.max	
pH 5.2	427-431 nm
pH 6.8	588-590 nm

1	gm	0.50
5	gm	2.00

T 21866 Bromocresol purple indicator solution standard

pH transition range:

pH 5.2 to 6.8 — Greenish yellow to blue violet

125	ml	1.00
4x125	ml	3.00

T 23304 Bromophenol blue ACS/AR pH indicator

CAS 115-39-9

$C_{19}H_{10}O_5SBr_4$ — F.W.669.98

Clarity of solution	Passes test
Visual transition interval	pH 3.0 to pH 4.6 (Yellow to blue)

5	gm	1.50
25	gm	5.50

T 23309 Bromophenol blue indicator solution

125	ml	1.00
4X125	ml	3.00

T 23320 Bromophenol Red Lab-Grade

pH 5.2-7.0, yellow-reddish purple

5	gm	5.50
25	gm	17.25

T 23325 Bromophenol red indicator solution

125	ml	1.00
4X125	ml	3.00

T 23401 Bromothymol Blue powder Lab-Grade

CAS 76-59-5

F.W. 624.40

$C_{27}H_{28}Br_2O_5S$

pH transition range:

pH 5.8 - 7.6	yellow -blue
Abs. max:	
pH 5.8	430-435 nm
pH 7.6	615-618 nm

1	gm	0.90
5	gm	3.40

T 23406 Bromo Thymol blue indicator solution

125	ml	1.05
4X125	ml	3.15

T 23370 Buffer Tablet pH 4.0 Lab-Grade

10	tab	1.45
10x10	tab	13.00

T 23375 Buffer Tablet pH 7.0 Lab-Grade

10	tab	1.45
10x10	tab	13.00

T 23380 Buffer Tablet pH 9.2 Lab-Grade

10	tab	1.45
10x10	tab	13.00

T 24869 n-Butyl acetate Lab-Grade

CAS 123-86-4

UN-1123 IMDG - 3.2/II

$CH_3COO(CH_2)_3CH_3$ — 97% — F.W.116.16

500	ml	3.10

T 24874 n-Butyl acetate ACS/AR

CAS 123-86-4

UN- 1123 IMDG - 3.2/II

$CH_3COO(CH_2)_3CH_3$ — 99.5% — F.W.116.16

Maximum Limits

Color (APHA)	10
Residue after Evaporation	0.001%
Titrable acid	0.0016 meq/g
Substances Darkened by sulfuric acid	Passes test
Water (H_2O)	0.1%
n-Butyl alcohol (C_4H_9OH)	0.2%
n-Butyl formate ($HCOOC_4H_9$)	0.1%
n-Butyl propionate ($C_2H_5COOC_4H_9$)	0.1%

500	ml	11.00
6x500	ml	55.00

T 24458 n-Butyl alcohol Lab-Grade

CAS 71-36-3

UN -1120 IMDG - 3.3 /III

$(CH_3)(CH_2)_3OH$ — 98% — F.W.74.12

500	ml	2.40
2.5	lt	11.00

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 24463 n-Butyl alcohol ACS/AR

CAS 71-36-3
UN-1120 IMDG - 3.3/III

$(CH_3)(CH_2)_3OH$		99.5%	F.W.74.12
Maximum Limits			
Color (APHA)			10
Residue after Evaporation			0.005%
Titrable acid			0.0008 meq/g
Aldehydes			Passes test
Butyl ether			0.2%
Water (H_2O)			0.1%
500	ml		4.70
6x500	ml		23.70
2.5	lt		20.00

T 24466 n-Butyl alcohol for spectroscopy

CAS 71-36-3
UN-1120 IMDG - 3.8 /III

$(CH_3)(CH_2)_3OH$		99.7%	F.W.74.12
500	ml		6.50

T 112577 iso-Butyl alcohol Lab-Grade

CAS 78-83-1

$(CH_3)_2CH.CH_2OH$		99%	F.W.74.12
500	ml		2.40

T 112582 iso-Butyl alcohol ACS/AR

CAS 78-83-1

$(CH_3)_2CH.CH_2OH$		99%	F.W.74.12
Solubility in water			Passes test
Maximum Limits			
Color (APHA)			10
Residue after Evaporation			0.001%
Titrable acid			0.0005 meq/g
Water (H_2O)			0.1%
500	ml		3.70
6x500	ml		18.50

T 24740 tert-Butyl alcohol Lab-Grade

CAS 75-65-0

$(CH_3)_3COH$		98%	F.W.74.12
500	ml		4.70
6x500	ml		23.50

T 24745 tert-Butyl alcohol ACS/AR

CAS 75-65-0

$(CH_3)_3COH$		99.0%	F.W.74.12
Boiling range			Within 1.5°C including 82.0°C±0.1°C
Melting point			Min.24°C
Maximum Limits			
Residue after Evaporation			0.003%
500	ml		6.85
6x500	ml		34.25

T 26578 iso-Butyl methyl ketone Lab-Grade

CAS 108-10-1

$(CH_3)_2CHCH_2COCH_3$		99%	F.W.100.16
500	ml		2.60
2.5	lt		12.00

T 26583 iso-Butyl methyl ketone ACS/AR

CAS 108-10-1

$(CH_3)_2CHCH_2COCH_3$		99%	F.W.100.16
Appearance			Clear
Maximum Limits			
Color (APHA)			15
Residue after Evaporation			0.005%
Titrable acid			0.002 meq/g
Water			0.1%
500	ml		4.20
6x500	ml		21.00
2.5	lt		18.50

T 29038 Cadmium acetate dihydrate Lab-Grade

CAS 5743-04-4

$(CH_3COO)_2Cd.2H_2O$		98%	F.W.266.53
500	gm		15.10

T 29043 Cadmium acetate dihydrate ACS/AR

CAS 5743-04-4

$(CH_3COO)_2Cd.2H_2O$		99%	F.W.266.52
Maximum Limits			
Chloride (Cl)			0.001%
Insoluble matter			0.010%
Iron (Fe)			0.001%
Lead (Pb)			0.005%
Sulfate (SO_4)			0.005%
250	gm		12.50
500	gm		24.00

T 29084 Cadmium carbonate Lab-Grade

CAS 513-78-0

$CdCO_3$		62-66%	F.W.172.42
500	gm		21.40

T 29097 Cadmium chloride hydrated Lab-Grade

CAS 7790-78-5

$CdCl_2.2^1/_2H_2O$		99%	F.W.228.35
100	gm		7.50
500	gm		35.50

T 29102 Cadmium chloride hydrate ACS/AR

CAS 7790-78-5

$CdCl_2.2^1/_2H_2O$		99.5%	F.W.228.35
Maximum Limits			
Insoluble matter			0.005%
Nitrate and Nitrite (as NO_3)			0.003%
Sulfate (SO_4)			0.005%
Ammonium (NH_4)			0.005%
Copper (Cu)			0.0005%
Iron (Fe)			0.0005%
Lead (Pb)			0.005%
Substances not Pptd. by Hydrogen sulfide (as sulfates)			0.2%
Zinc (Zn)			0.1%
100	gm		11.50
500	gm		45.70

T 29328 Cadmium nitrate Lab-Grade

CAS 10022-68-1

$Cd(NO_3)_2.4H_2O$		99%	F.W.308.48
100	gm		3.00
500	gm		13.40

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 29333 Cadmium nitrate ACS/AR

CAS 10022-68-1

$Cd(NO_3)_2.4H_2O$	99%	F.W.308.47
Maximum Limits		
Ammonium (NH_4)		0.003%
Chloride (Cl)		0.005%
Copper (Cu)		0.002%
Insoluble matter		0.005%
Iron (Fe)		0.001%
Lead (Pb)		0.005%
Sulfate (SO_4)		0.003%
Zinc (Zn)		0.05%

500	gm	23.50

T 29474 Cadmium sulfate Lab-Grade

CAS 7790-84-3

$3CdSO_4.8H_2O$	98-103%	F.W.769.52

500	gm	15.10

T 29479 Cadmium sulfate ACS/AR

CAS 7790-84-3

$3CdSO_4.8H_2O$	99%	F.W.769.52
Maximum Limits		
Insoluble matter		0.005%
Loss on drying at 150°C		1.0%
Chloride (Cl)		0.001%
Nitrate and Nitrite (as NO_3)		0.003%
Arsenic (As)		0.0002%
Copper (Cu)		0.002%
Iron (Fe)		0.001%
Lead (Pb)		0.003%
Substances not Pptd. by Hydrogen sulfide (as Sulfates)		0.15%
Zinc (Zn)		0.1%

500	gm	21.40

T 29946 Calcium carbonate extra pure Lab-Grade

CAS 471-34-1

$CaCO_3$	98.5%	F.W.100.09
Maximum Limits		
Acid insoluble substances		0.2%
Arsenic (As)		0.0003%
Fluoride (F)		0.005%
Heavy metals (as Pb)		0.002%
Lead (Pb)		0.0003%
Loss on drying @200°C		2%
Magnesium and Alkali salts		1%

500	gm	1.40

T 29951 Calcium carbonate precipitated ACS/AR

CAS 471-34-1

$CaCO_3$	99.0%	F.W.100.09
Maximum Limits		
Insoluble in dilute hydrochloric acid		0.01%
Ammonium hydroxide Ppt.		0.01%
Water soluble titrable base		0.002 meq/g
Chloride (Cl)		0.001%
Fluoride (F)		0.0015%
Oxidizing substances (as NO_3)		0.005%
Copper (Cu)		0.002%
Sulfate (SO_4)		0.01%
Ammonium (NH_4)		0.003%
Barium (Ba)		0.005%
Heavy metals (as Pb)		0.001%
Iron (Fe)		0.003%
Magnesium (Mg)		0.02%
Potassium (K)		0.01%
Sodium (Na)		0.1%
Strontium (Sr)		0.1%

500	gm	4.80
6x500	gm	24.00

T 29962 Calcium chloride dihydrate Lab-Grade

CAS 10035-04-8

$CaCl_2.2H_2O$	99.0-107.0%	F.W.147.01
Maximum Limits		
Arsenic (as As)		0.0003%
Fluoride (F)		0.004%
Heavy metals (as Pb)		0.002%
Lead (Pb)		0.0005%
Magnesium and Alkali Salts		4.0%

500	gm	2.50

T 31804 Carbon Disulfide Lab-Grade

CAS 75-15-0

CS_2

UN-1131 IMDG - 3.1/I

	F.W. 76.14
Assay	min. 99.9%
Boiling Range	45-47.5 deg C (95%)

500	ml	2.40

T 30408 Calcium hydroxide Lab-Grade

CAS 1305-62-0

$Ca(OH)_2$	90%	F.W.74.09

500	gm	2.45

T 30413 Calcium hydroxide ACS/AR

CAS 1305-62-0

$Ca(OH)_2$	95-98%	F.W.74.09
Maximum Limits		
Insoluble in Hydrochloric acid		0.03%
Chloride (Cl)		0.03%
Sulfur compounds (as SO_4)		0.1%
Heavy metals (as Pb)		0.003%
Iron (Fe)		0.05%
Magnesium and Alkali salts (as Sulphate)		1.0%

500	gm	8.50

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 30833 Calcium oxide selected lumps ACS/AR

CAS 1305-78-8

CaO	95.0%	F.W.56.08
Maximum Limits		
Ammonium hydroxide Ppt.		1.0%
Chloride (Cl)		0.005%
Heavy metals (as Pb)		0.01%
Insoluble in acetic acid		1.0%
Iron (Fe)		0.1%
Loss on Ignition		5.0%
Nitrate (NO_3)		0.01%
Sulfate (SO_4)		0.1%
Zinc (Zn)		0.015%

500	gm	7.70
6x500	gm	38.50

T 30830 Calcium oxide powder Lab-Grade

CAS 1305-78-8

CaO	95%	F.W.56.08

500	gm	1.90

T 31196 Calcium sulfate dihydrate ACS/AR

CAS 10101-41-4

$CaSO_4.2H_2O$	98.0-102.0%	F.W.172.17
Maximum Limits		
Insoluble in dilute Hydrochloride acid		0.02%
Chloride (Cl)		0.005%
Nitrate (NO_3)		To pass test (limit about 0.005%)
Carbonate (CO_3)		To pass test
Heavy metals (as Pb)		0.002%
Iron (Fe)		0.001%
Magnesium and alkali salts (as Sulfate)		0.3%

500	gm	9.35
6x500	gm	46.75

T 31201 Carbol Fuchsin powder Lab-grade

CAS 4197-24-4

1	gm	0.25
5	gm	1.00

T 31254 Casein Soluble Lab-Grade

CAS 9005-46-3-

Nitrogen content	min. 12.0%
LOD (105 deg C)	7.0%

500	gm	10.80

T 31206 Carbol Fuchsin (Dilute) staining solution (Ziehl Neelsen strong solution)

125	ml	1.05
4X125	ml	3.15

T 31221 Carbol Fuchsin (Strong) staining solution (Ziehl Neelsen strong solution)

125	ml	1.25
4X125	ml	3.75

T 31250 Carmine Lab-Grade

C.I. NO. 75470
CAS 1390-65-4

Carminic acid (spectro)	~ 50%
Absorption max. (DMSO)	565-570 (525-532) nm

1	gm	2.50
5	gm	9.70

T 31858 Carbon Tetra Chloride Lab-Grade

CAS 56-23-5

CCl_4	99.9%	F.W.153.82

UN-1846 IMDG-6.1/II

500	ml	2.60
12x500	ml	27.00
1	lt	4.70
2.5	lt	10.90

T 31863 Carbon Tetra Chloride ACS/AR

CAS 56-23-5

CCl_4	99.9%	F.W.153.82

UN-1846 IMDG-6.1/II

Maximum Limits	
Color (APHA)	10
Residue after evaporation	0.001%
Water soluble titrabic acid	0.0005 meq/g
Free chlorine (Cl)	Passes test
Sulfur compounds (as S)	Passess test (limit about 0.005%)
Iodine-Consuming substances	Passes test
Substances darkened by sulfuric acid	passes test
Suitability for use in dithizone test	passes test

500	ml	3.00
6x500	ml	15.00
2.5	lt	11.90

T 31883 Carbon Tetra Chloride for spectro Scopy

CAS 56-23-5

CCl_4	99.9%	F.W.153.82

UN-1846 IMDG-6.1/II

Ultraviolet absorbance (1cm cell vs. water)

(nm)	265	270	280	290	300	330-400
Limit	1.00	0.35	0.10	0.05	0.02	0.01

Maximum Limits	
Color (APHA)	10
Residue after Evaporation	0.001%
Water-soluble titrable acid	0.005 meq/g
Free Chlorine (Cl)	passes test
Sulfur compounds (as S)	passes test (limit about 0.005%)
Iodine Consuming substances	passes test
Substance darkened by Sulfuric acid	passes test
Suitability for use in Dithizone tests	passes test

500	ml	11.00

T 31893 Carbon Tetra Chloride for HPLC

CAS 56-23-5

CCl_4	99.9%	F.W.153.82

UN-1846 IMDG-6.1/II

500	ml	5.50

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 32555 Chlorine Water saturated Lab-Grade

500	ml		1.20

T 32428 Ceric sulfate Lab-Grade

CAS 13590-82-4

$Ce(SO_4)_2.4H_2O$	85%	F.W.528.43
Maximum Limits		
Insoluble matter		0.1%
Iron (Fe)		0.1%
Phosphate (PO_4)		0.1%

100	gm	6.40

T 32433 Ceric sulfate ACS/AR

CAS 13590-82-4

$Ce(SO_4)_2.4H_2O$	94%	F.W.528.43
Maximum Limits		
Insoluble matter		0.1%
Chloride (Cl)		0.001%
Iron (Fe)		0.1%
Phosphate (PO_4)		0.01%

100	gm	7.00

T 33416 mono-Chlorobenzene ACS/AR

CAS 108-90-7
UN - 1134 IMDG 0 3.3/III

C_6H_5Cl	99%	F.W.112.56
Maximum Limits		
Color (APHA)		30%
Residue after evaporation		0.02%
Titrable acid		0.004 meq/g

500	ml	4.50
6x500	ml	22.50

T 36355 p-Chlorobenzoic acid Lab-Grade

CAS 74-11-3

ClC_6H_4COOH	99%	F.W.156.57

100	gm	3.00
500	gm	11.40

T 35400 Chloroform Lab-Grade

CAS 67-66-3
UN - 1888 IMDG - 6.1/III

$CHCl_3$	99.5%	F.W.119.38

500	ml	2.80
6x500	ml	14.00
1	lt	5.00
2.5	lt	11.50

T 35405 Chloroform ACS/AR

CAS 67-66-3
UN - 1888 IMDG - 6.1/III

$CHCl_3$	99.0-99.4%	F.W.119.38
Maximum Limits		
Color (APHA)		10%
Residue after evaporation		0.001%
Acetone and Aldehyde [as $(CH_3)_2CO$]		Passes test (limit about 0.005%)
Acid and Chloride		Passes test
Free chlorine (Cl)		Passes test
Lead (Pb)		0.05 ppm
Substances darkened by sulfuric acid		Passes test
Suitability for use in dithizone tests		Passes test

500	ml	4.25
6x500	ml	21.25
1	lt	8.25
2.5	lt	18.80

T 39003 Chromium (III) chloride hexahydrate Lab-Grade

500	gm	19.25
6x500	gm	

T 39008 Chromium (III) chloride hexahydrate ACS/AR

CAS 10060-12-5

$CrCl_3.6H_2O$	99.0%	F.W.266.45
Maximum Limits		
Insoluble matter		0.01%
Sulfate (SO_4)		0.01%
Iron (Fe)		0.01%

500	gm	30.25
6x500	gm	151.25

T 39068 Chromium (III) nitrate nonahydrate Lab-Grade

CAS 7789-02-8

$Cr(NO_3)_3.9H_2O$	99%	F.W.400.15

500	gm	26.10
6x500	gm	130.50

T 39082 Chromium (III) oxide green Lab-Grade

CAS 1308-38-9

Cr_2O_3	99%	F.W.151.99

500	gm	6.50

T 39087 Chromium (III) oxide green ACS/AR

CAS 1308-38-9

Cr_2O_3	99%	F.W.151.99
Maximum Limits		
Water soluble salts (Wt.%)		0.2%

500	gm	15.00

T 38976 Chromium trioxide Lab-Grade

CAS 1333-82-0
UN - 1463 IMDG - 5.1/II

CrO_3	99%	F.W.99.99

500	gm	4.25

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 38981 Chromium trioxide ACS/AR

CAS 1333-82-0
UN-1463 IMDG - 5.1/II
CrO_3 99.0% F.W.99.99

Maximum Limits

Insoluble matter	0.01%
Chloride (Cl)	0.005%
Nitrate (NO_3)	0.05%
Sulfate (SO_4)	0.005%
Sodium (Na)	0.2%
Iron, Aluminium, Barium	0.03%

500 gm 19.25
6x500 gm

T 39570 Cinnamic acid Lab-Grade

CAS 140-10-3
$C_6H_5CH{:}CHCOOH$ 99% F.W.148.16

500 gm 21.40

T 39793 Citric acid anhydrous Lab-Grade

CAS 5949-29-1
$C_6H_8O_7$ 99.5% F.W.210.14

500 gm 4.10
6X500 gm 20.50

T 39798 Citric acid anhydrous ACS/AR

CAS 5949-29-1
$C_6H_8O_7$ 99.7% F.W.210.14

Maximum Limits

Insoluble matter	0.005%
Residue after Ignition	0.02%
Chloride (Cl)	0.001%
Oxalate (C_2O_4)	Passes test (limit about 0.05%)
Phosphate (PO_4)	0.001%
Sulfate (SO_4)	0.002%
Iron (Fe)	3 ppm
Lead (Pb)	2 ppm
Substances carbonizable by Hot sulfuric acid (Tartrates, etc.)	Passes test

500 gm 6.25
6x500 gm 31.25

T 39796 Citric acid monohydrate Lab-Grade

CAS 5949-29-1
$C_6H_8O_7.H_2O$ 99% F.W.210.14

500 gm 4.40

T 39801 Citric acid monohydrate ACS/AR

CAS 5949-29-1
$C_6H_8O_7.H_2O$ 99.0-102.0% F.W.210.14

Maximum Limits

Insoluble matter	0.005%
Residue after Ignition	0.02%
Chloride (Cl)	0.001%
Oxalate (C_2O_4)	Passes test (limit about 0.05%)
Phosphate (PO_4)	0.001%
Sulfate (SO_4)	0.002%
Iron (Fe)	3 ppm
Lead (Pb)	2 ppm
Substances carbonizable by Hot sulfuric acid (Tartrates, etc.)	Passes test

500 gm 6.80
6x500 gm 34.00

T 40100 Cobalt (II) acetate tetrahydrate Lab-Grade

CAS 6147-53-1
$(CH_3COO)_2Co.4H_2O$ 99.0% F.W.249.08

500 gm 39.00
6x500 gm 195.00

T 40178 Cobalt (II) Chloride Lab-Grade

CAS 7791-13-1
$CoCl_2.6H_2O$ F.W.237.93

Assay (ex co)	Min. 98%
Sulphate	0.03%
Iron	0.01%

100 gm 9.40

T 40390 Cobalt oxide ACS/AR

CAS 1308-06-1
Co_3O_4 70.0% F.W.240.8

Maximum Limits

Chloride (Cl)	0.01%
Iron (Fe)	0.1%
Nickel (Ni)	0.2%
Substances not Pptd. by $(NH_4)_2S$	0.5%
Sulfate (SO_4)	0.2%

50 gm 82.50

T 40484 Cobalt (II) sulfate heptahydrate Lab-Grade

CAS 10026-24-1
$CoSO_4.7H_2O$ 98.0% F.W.281.0

500 gm 35.70
6x500 gm 178.50

T 40489 Cobalt (II) sulfate heptahydrate ACS/AR

CAS 10026-24-1
$CoSO_4.7H_2O$ 99% F.W.281.0

Maximum Limits

Chloride (Cl)	0.001%
Copper (Cu)	0.002%
Insoluble matter	0.01%
Lead (Pb)	0.005%
Nickel (Ni)	0.1%
Substances not Pptd. by $(NH_4)_2S$	0.2%
Zinc (Zn)	0.02%

500 gm 45.00

T 40715 Congo red pH indicator Lab-Grade

CAS 57[illegible]-58-0 [C.I.22120]
$C_{32}H_{22}N_6Na_2O_6S_2$ F.W.696.68
Absorption Max.(in water plus 1ml 1% Na_2CO_3) 497 nm

25 gm 1.00
100 gm 3.50

T 40720 Congo Red indicator solution

125 ml 1.00
4x125 ml 3.00

T 40725 Cotton Blue indicator solution

125 ml 3.00
4x125 ml 9.00

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 41200 Cotton Blue for m.s Lab-Grade

25	gm	4.70
100	gm	14.25

T 41215 o-Cresol Lab-Grade

CAS 95-48-7
UN - 2076 IMDG - 6.1 /II
$CH_3C_6H_4OH$ 99% F.W.108.14

500	ml	5.70
6x500	ml	28.50

T 41222 p-Cresol Lab-Grade

CAS 106-44-5
UN - 2076 IMDG - 6.1/II
$CH_3C_6H_4OH$ 99% F.W.108.14

500	ml	8.50

T 41283 Cresol red pH indicator Lab-Grade

CAS 1733-12-6
$C_{21}H_{18}O_5S$ F.W.382.44
Absorption Max.(in Borate Buffer; pH 9).. 570 (367) nm
Visual Transition intervals pH 2.0 to pH 3.0 (Orange to Yellow)
pH 7.2 to pH 8.8 (Yellow to Red)

5	gm	1.10
25	gm	4.25

T 41327 Crystal violet for microscopy Lab-Grade

CAS 548-62-9 [C.I.42555]
$C_{25}H_{30}ClN_3$ 96-100.5.0% F.W.407.99
Maximum Limits

Water	7.5%
Residue on Ignition	1.5%
Alcohol-Insoluble substances	1.0%
Arsenic (As)	0.001%
Lead (Pb)	0.003%
Zinc (Zn)	0.05%

25	gm	1.50
100	gm	4.70

T 41242 Crystal violet staining solution (gram's)

125	ml	1.10
4x125	ml	3.30

T 41648 Cupric carbonate basic Lab-Grade

CAS 12069-69-1
$CuCO_3.Cu(OH)_2H_2O$ F.W.239.10

500	gm	7.10
6x500	gm	35.50

T 41662 Cupric chloride dihydrate Lab-Grade

CAS 10125-13-0
UN - 2802 IMDG - 8/III
$CuCl_2.2H_2O$ 99% F.W.170.48

500	gm	6.25

T 41667 Cupric chloride dihydrate ACS/AR

CAS 10125-13-0
UN-2802 IMDG-8/III
$CuCl_2.2H_2O$ 99.0% F.W.170.48
Maximum Limits

Insoluble matter	0.01%
Nitrate (NO_3)	0.015%
Sulfate (SO_4)	0.005%
Substances not Pptd. by hydrogen sulfide (as Sulfate)	0.10%
Iron (Fe)	0.005%
Ammonium sulfide metals other than Iron	0.01%

500	gm	14.50
6x500	gm	72.50

T 41876 Cupric nitrate trihydrate Lab-Grade

CAS 3251-23-8
$Cu(NO_3)_2.3H_2O$ 99.0% F.W.241.60

500	gm	5.00

T 41881 Cupric nitrate trihydrate ACS/AR

CAS 3251-23-8
$Cu(NO_3)_2.3H_2O$ 99.5% F.W.241.60
Maximum Limits

Insoluble matter	0.01%
Chloride (Cl)	0.002%
Sulfate (SO_4)	0.01%
Substances not Pptd. by hydrogen sulfide (as Sulfate)	0.05%
Lead (Pb)	0.001%
Iron (Fe)	0.005%
Ammonium sulfide metals other than Iron (as Ni)	Passes test (limit about 0.01%)

500	gm	8.00
6x500	gm	40.00

T 41933 Cupric oxide Lab-Grade

CAS 1317-38-0
CuO 97% F.W.79.55

500	gm	14.25

T 41938 Cupric oxide ACS/AR

CAS 1317-38-0
CuO 99.0% F.W.79.55
Maximum Limits

Insoluble in dilute Hydrochloric acid	0.02%
Carbon compounds (as C)	0.01%
Chloride (Cl)	0.005%
Nitrogen compounds (as N)	0.002%
Sulphur compounds (as SO_4)	0.02%
Free Alkali	Passes test
Sulfate (SO_4)	0.01%
Substances not Pptd. by hydrogen sulfide (as Sulfate)	0.2%
Ammonium hydroxide precipitate	0.1%

500	gm	45.60
6x500	gm	228.00

T 42139 Cupric sulfate penta hydrate Lab-Grade

CAS 7758-99-8
$CuSO_4.5H_2O$ 99% F.W.249.68

500	gm	2 30
6x500	gm	14.00

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T. BAKER LAB CHEMICALS

T 42144 Cupric sulfate ACS/AR

CAS 7758-99-8
$CuSO_4.5H_2O$ 99.5% F.W.249.68

Maximum Limits

Insoluble matter	0.005%
Chloride (Cl)	0.001%
Nitrogen compounds (as N)	0.001%
Substances not Pptd. by hydrogen sulfide (as Sulfates)	0.1%
Iron (Fe)	0.003%
Ammonium sulfide metals other than Iron	0.005%

500	gm	4.50
6x500	gm	

T 43206 Cyclohexane Lab-Grade

CAS 110-82-7
UN - 1145 IMDG - 3.1/II
C_6H_{12} 99.0% F.W.84.16

500	ml	3.75

T 43211 Cyclohexane ACS/AR

CAS 110-82-7
UN - 1145 IMDG 3.1/II
C_6H_{12} 99.0% F.W.84.16
Appearance Clear

Maximum Limits

Color (APHA)	10
Residue after evaporation	0.002%
Substances darkened by sulfuric acid	Passes test
Water (H_2O)	0.02%

500	ml	6.00

T 43221 Cyclohexane for spectroscopy

CAS 110-82-7
UN - 1145 IMDG - 3.1/II
C_6H_{12} 99.7% F.W.84.16
Ultraviolet absorbance (1cm cell vs.water)

λ(nm)	210	220	230	240	250	260	300-400
Limit	1.00	0.50	0.20	0.08	0.03	0.02	0.01

Maximum Limits

Color (APHA)	10
Residue after Evaporation	0.001%
Substances Darkened by Sulfuric acid	Passes test
Water	0.02%

500	ml	7.50
6x500	ml	37.50

T 43316 Cyclohexanone Lab-grade

CAS 108-94-1
UN - 1915 IMDG - 3.3/III
$C_6H_{10}O$ 99.0% F.W.98.15

500	ml	3.60
2.5	lt	16.00

T 43321 Cyclohexanone ACS/AR

CAS 108-94-1
UN - 1915 IMDG- 3.3/III
$C_6H_{10}O$ 99.5% F.W.98.15
Appearance Clear

Maximum Limits

Color (APHA)	10
Residue after evaporation	0.05%
Water (H_2O)	0.05%

500	ml	6.80
12x500	ml	74.00

T 46192 Dextrine white Lab-Grade

CAS 9004-53-9
$(C_6H_{10}O_5)_n$-xH_2O

500	gm	4.80

T 83600 Dextrose anhydrous Lab-Grade

CAS 50-99-7
$C_6H_{12}O_6$ F.W.180.16

500	gm	1.55
5	kg	13.00

T 83605 Dextrose anhydrous ACS/AR

CAS 50-99-7
$C_6H_{12}O_6$ F.W.180.16
Specific rotation, $[\alpha]_D^{25°}$ +52.5° to +53.0°

Maximum Limits

Insoluble matter	0.005%
Loss on drying @ 105°C	0.2%
Residue after Ignition	0.02%
Titrable acid	0.002 meq/g
Chloride (Cl)	0.01%
Sulfate and sulfite (as SO_4)	0.005%
Starch	Passes test
Heavy metals (as Pb)	5 ppm
Iron (Fe)	5 ppm

500	gm	1.80
6x500	gm	9.00

T 83612 Dextrose monohydrate ACS/AR

CAS 5996-10-1
$C_6H_{12}O_6.H_2O$ F.W.198.17

Maximum limits

Arsenic (As)	0.00002%
Chloride (Cl)	0.005%
Heavy metals (as Pb)	0.0005%
Insoluble matter	0.005%
Iron (Fe)	0.0005%
Starch	Passes test
Sulfate and sulfite (as SO_4)	0.005%

500	gm	1.75
6x500	gm	8.75

T 54480 Diazo A Reagent indicator solution

125	ml	2.50
4x125	ml	7.50

T 54485 Diazo B Reagent indicator solution

125	ml	2.50
4x125	ml	7.50

T 54493 Diethanolamine Lab-Grade

CAS 111-42-2
$C_4H_{11}NO_2$ 98% F.W.105.14

500	ml	4.80
6x500	ml	24.00

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T. BAKER LAB CHEMICALS

T 54498 Diethanolamine ACS/AR

CAS 111-42-2

$C_4H_{11}NO_2$	99.5%	F.W.105.14
Apparent equivalent weight		104.0-106.0
Maximum Limits		
Color (APHA)		15
Residue after Ignition		0.005%
Monoethanolamine		1.0%
Triethanolamine		1.0%
Water (H_2O)		0.15%

500	ml	8.80
6x500	ml	44.00

T 55059 Diethylamine Lab-Grade

CAS 109-89-7
UN - 1154 IMDG -3.1/II

$(C_2H_5)_2NH$	99.5%	F.W.73.14

500	ml	4.10
6x500	ml	20.50
2.5	lt	18.00

T 55064 Diethylamine ACS/AR

CAS 109-89-7
UN - 1154 IMDG -3.1/II

$(C_2H_5)_2NH$	99.5%	F.W.73.14

500	ml	7.10
6x500	ml	35.50

T 56000 Diethyl ether Lab-Grade

CAS 60-29-7
UN-1155 IMDG - 3.1/I

$(C_2H_5)_2O$	98%	F.W.74.12

500	ml	3.50
2.5	lt	15.25

T 56005 Diethyl ether ACS/AR

CAS 60-29-7
UN-1155 IMDG - 3.1/I

$(C_2H_5)_2O$	F.W.74.12
Peroxide Inhibitor (BHT)	0.0001%
Maximum Limits	
Color (APHA)	10
Peroxide (as H_2O_2)	1 ppm
Residue after Ignition	0.001%
Titrable acid	0.0002 meq/g
Carbonyl (as HCHO)	0.001%
Substances darkened by sulfuric acid	Passes test

500	ml	4.20
6x500	ml	21.00
2.5	lt	19.50

T 63713 Dimethyl glyoxime ACS/AR

CAS 95-45-4

$(CH_3C(NOH)C(NOH)CH_3$	99%	F.W.116.12
Melting point		Approx.240°C
Suitability for nickel determination		Passes test
Maximum Limits		
Insoluble in alcohol		0.05%
Residue after Ignition		0.05%

100	gm	6.10

T 65530 Dimethyl sulfoxide Lab-Grade

CAS 67-68-5

CH_3SOCH_3	99%	F.W.78.13

500	ml	7.70
6x500	ml	38.70
2.5	lt	36.70

T 65535 Dimethyl sulfoxide ACS/AR

CAS 67-68-5

CH_3SOCH_3	99.5%	F.W.78.13
Appearance		Clear
Maximum Limits		
Residue after evaporation		0.01%
Titrable acid		0.001 meq/g
Substances darkened by Potassium hydroxide		Passes test
Water (H_2O)		0.1%

500	ml	9.40
6x500	ml	47.00

T 66152 m-Dinitrobenzene for synthesis Lab-Grade

CAS 99-65-0
UN-1597 IMDG - 6.1/II

$C_6H_4(NO_2)_2$	98%	F.W.168.11

500	gm	9.60

T 66183 3-5-Dinitrobenzoic acid Lab-Grade

CAS 99-34-3

$C_7H_4N_2O_6$	99.5%	F.W.212.12

500	gm	10.70

T 66889 1,4-Dioxan Lab-Grade

CAS 123-91-1
UN -1165 UMDG - 3.2/II

$C_4H_8O_2$	99%	F.W.88.11

500	ml	8.25
6x500	ml	41.25

T 66894 1,4-Dioxan ACS/AR

CAS 123-91-1

$C_4H_8O_2$	99.5%	F.W.88.11
Freezing point		Min. 11.0°C
Maximum Limits		
Color (APHA)		20
Peroxide (as H_2O_2)		0.005%
Residue after evaporation		0.005%
Titrable acid		0.0016 meq/g
Carbonyl (as HCHO)		0.01%
Water (H_2O)		0.05%

500	ml	9.70
2.5	lt	42.50

T 67430 Diphenyl Lab-Grade

CAS 92-52-4

$C_{12}H_{10}$	98%	F.W.154.21

100	gm	3.40

T. BAKER LAB CHEMICALS

T 67517 Diphenylamine ACS/AR

CAS 122-39-4
$(C_6H_5)_2NH$ 99% F.W.169.23
Melting point 52.5°-54.0°C
Senstitivity to nitrate Passes test
Solubility in alcohol Passes test
Maximum Limits
Residue after Ignition 0.03%
Nitrate (NO_3) Passes test

100 gm 5.70
6x100 gm 28.50

T 68710 D.P.X. Mountant Lab-Grade

Refractive index $(n)^{20}D$ 1.515-1. 525

250 ml 4.40

T 68775 Drabkin's Reagent

125 ml 1.50
4x125 ml 4.50

T 68725 Ehlrich's Reagent

125 ml 1.50
4x125 ml 4.50

T 70900 Eosin blue for microscopy Lab-Grade

CAS 548-24-3 [45400]
$C_{20}H_6Br_2N_2Na_2O_9$ F.W.624.09

25 gm 3.10
100 gm 10.50

T 70905 Eosin Blue stain solution (2% w/v)

125 ml 1.05
4x125 ml 3.15

T 71296 Eosin yellow for microscopy Lab-Grade

CAS 548-26-5 [45380]
$C_{20}H_6Br_4Na_2O_5$ F.W.691.86

25 gm 3.15
100 gm 10.00

T 71300 Eosin Yellow stain solution (2% w/v)

125 ml 1.05
4x125 ml 3.15

T 71800 Eriochrome Black T Indicator solution

125 ml 1.50
4x125 ml 4.50

T 71803 Eriochrome black T ACS/AR

CAS 1787-61-7 [14645]
$C_{22}H_{12}N_3NaO_7S$ F.W.461.38
Clarity of solution Passes test
Suitability as complexometric indicator Passes test

25 gm 2.55
100 gm 7.80

T 71815 Esbach's Reagent indicator solution

125 ml 1.40
4x125 ml 4.20

T 71972 mono-Ethanolamine Lab-grade

CAS 141-43-5
UN-2491 IMDG - 8/III
$CH_2OHCH_2NH_2$ 99% F.W.61.08

500 ml 4.45

T 71977 mono-Ethanolamine ACS/AR

CAS 141-43-5
UN-2491 IMDG - 8/III
$CH_2OHCH_2NH_2$ 99% F.W.61.08
Maximum Limits
Color (APHA) 15
Iron (Fe) 5 ppm
Heavy metals (as Pb) 5 ppm
Water (H_2O) 0.30%

500 ml 6.35

T 76672 Ethyl acetate Lab-Grade

CAS 141-78-6
UN-1173 IMDG-3.2/II
$CH_3COOC_2H_5$ 99% F.W.88.11

500 ml 2.25
6x500 ml 11.25
2.5 lt 9.70

T 76677 Ethyl acetate ACS/AR

CAS 141-78-6
UN-1173 IMDG-3.2/II
$CH_3COOC_2H_5$ 99% F.W.88.11
Maximum Limits
Color (APHA) 10
Residue after evaporation 0.003%
Water (H_2O) 0.2%
Titrable acid 0.0009 meq/g
Substances darkened by sulfuric acid Passes test

500 ml 4.00
6x500 ml 20.00
2.5 lt 18.50

T 51900 Ethylene Chloride Lab-Grade

CAS 107-06-2
$ClCH_2CH_2Cl$

F.W. 98.96
Assay (GC) Min. 99.0%
B.P. 82-84 deg C(95%)
Free Chlorine 0.002%

500 ml 2.10
6x500 ml 10.50
2.5 lt 10.00

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 74352 Ethylenediamine tetraacetic acid disodium salt ACS/AR

CAS 6381-92-6
$C_{10}H_{14}O_8Na_2N_2.2H_2O$ 98% F.W.372.24
pH of a 5% solution @ 25°C 4.0-6.0
Maximum Limits
Insoluble matter 0.005%
Nitrilotriacetic acid [$(HOCOCH_2)_3N$] 0.1%
Heavy metals (as Pb) 0.005%
Iron (Fe) 0.01%

100	gm	2.00
6x100	gm	10.00
500	gm	9.40
6x500	gm	47.00

T 74330 E.D.T.A. Solution N/10

125	ml	1.50
4x125	ml	4.50

T 74335 E.D.T.A. Solution N/50

125	ml	1.50
4x125	ml	4.50

T 71878 Ethylene glycol Lab-Grade

CAS 107-21-1
$CH_2(OH)CH_2OH$ 99% F.W.62.07

500	ml	2.60
2.5	lt	11.40

T 71883 Ethylene glycol ACS/AR

CAS 107-21-1
$CH_2(OH)CH_2OH$ 99% F.W.62.07
Specific gravity @ 20°/20°C 1.1151-1.1156
Maximum Limits
Color (APHA) 10
Residue after evaporation 0.005%
Acidity (as CH_3COOH) 0.005%
Chloride (Cl) 0.5 ppm
Iron (Fe) 0.1 ppm
Water (H_2O) 0.10%

500	ml	3.70
6x500	ml	18.50
2.5	lt	16.40

T 72344 Ethylene glycol monoethyl ether ACS/AR

CAS 110-80-5
UN-1171 IMDG - 3.3/III
$C_2H_5O.CH_2CH_2OH$ 99.5% F.W.90.12
Specific gravity @ 20°/20°C 0.9290-0.9330
Maximum Limits
Acidity (as CH_3COOH) 0.005%
Water (H_2O) 0.1%

500	ml	5.80
6x500	ml	29.00

T 106786 Ethylene glycol monomethyl ether Lab-Grade

CAS 109-86-4
UN -1188 IMDG - 3.3/III
$CH_3OCH_2CH_2OH$ 99% F.W.76.10

500	ml	5.00
2.5	lt	23.70

T 106791 Ethylene glycol monomethyl ether ACS/AR

CAS 109-86-4
UN - 1188 IMDG - 3.3/III
$CH_3OCH_2CH_2OH$ 99.5% F.W.76.10
Maximum Limits
Color (APHA) 10
Titrable acid 0.002 meq/g
Water (H_2O) 0.1%

500	ml	6.80
6x500	ml	34.00

T 106795 Eucalyptus Oil

125	ml	3.25
4x125	ml	9.75

T 79870 Fast Green indicator solution

125	ml	1.00
4x125	ml	3.00

T 79890 Fast Green (Malachite green) Lab-Grade

C.I. NO. 42000
F.W. 927.02
$C_{50}H_{52}N_4O_8$
Dye Content (Titanometry, dries) ~90%
Abs. max. (H_2O) 616-620 nm

1	gm	0.20
5	gm	0.80

T 79874 Fehling Solution 'A' Lab-Grade

500	ml	3.85

T 79878 Fehling Solution 'B' Lab-Grade

500	ml	7.10

T 79882 Ferric chloride anhydrous Lab-Grade

CAS 7705-08-0
UN-1173 IMDG - 8/III
$FeCl_3$ 96% F.W.162.21

500	gm	1.80

T 79887 Ferric chloride anhydrous ACS/AR

CAS 7705-08-0
UN - 1773 IMDG - 8/III
$FeCl_3$ 98% F.W.162.21
Maximum Limits
Alkalies and Earths (as SO_4) 0.3%
Copper (Cu) 0.05%
Ferrous chloride ($FeCl_2$) 1.5%
Insoluble in HCl 1.0%
Nitrate (NO_3) 0.01%
Phosphorous compounds (as PO_4) 0.03%
Sulfate (SO_4) 0.01%
Zinc (Zn) 0.05%

500	gm	16.50

T 79886 Ferric chloride hexahydrate Lab-Grade

CAS 10025-77-1
$FeCl_3.6H_2O$ 97% F.W.270.3

500	gm	5.40

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 79891 Ferric chloride hexahydrate ACS/AR

CAS 10025-77-1
$FeCl_3.6H_2O$ 98% F.W.270.3

Maximum Limits

Insoluble matter	0.01%
Nitrate (NO_3)	0.01%
Phosphorous compounds (as PO_4)	0.01%
Sulfate (SO_4)	0.01%
Copper (Cu)	0.003%
Ferrous Iron (Fe^{+2})	Passes test (limit about 0.002%)
Substances not Pptd. by Ammonium hydroxide (as Sulfates)	0.1%
Zinc (Zn)	0.003%

500	gm	10.00

T 80178 Ferric nitrate Lab-Grade

CAS 7782-61-8
UN - 1466 IMDG - 5.1/III
$Fe(NO_3)_3.9H_2O$ 98% F.W.404.0

Maximum Limits

Ferrous iron	0.01%
Chloride (Cl)	0.01%

500	gm	2.00

T 80655 Ferrous sulfate heptahydrate Lab-Grade

CAS 7782-63-0
$FeSO_4.7H_2O$ 99% F.W.278.01

500	gm	1.25

T 80660 Ferrous sulfate heptahydrate ACS/AR

CAS 7782-63-0
$FeSO_4.7H_2O$ 99.0% F.W.278.02

Maximum Limits

Insoluble matter	0.01%
Chloride (Cl)	0.001%
Phosphate (PO_4)	0.001%
Copper (Cu)	0.005%
Ferric Iron (Fe^{3+})	0.1%
Manganese (Mn)	0.05%
Substances not Pptd. by Ammonium hydroxide	0.05%
Zinc (Zn)	0.005%

500	gm	5.50
6x500	gm	27.50

T 81852 Formaldehyde solution 37-41% w/v ACS/AR

CAS 50-00-0
UN - 1198 IMDG - 3.3/III
HCHO 37-41% F.W.30.03
Preservative (CH_3OH) 10-15%

Maximum Limits

Color (APHA)	10
Residue after Ignition	0.005%
Titrable acid	0.006 meq/g
Chloride (Cl)	5 ppm
Sulfate (SO_4)	0.002%
Heavy metals (as Pb)	5 ppm
Iron (Fe)	5 ppm

500	ml	1.20
6x500	ml	6.00
2.5	lt	5.00

T 81971 Formic acid 85% Lab-Grade

CAS 64-18-6
UN - 1779 IMDG - 8/II
HCOOH 85% F.W. 46.03
Dilution test Passes test

Maximum Limits

Acetic acid	0.4%
Heavy metal (as Pb)	0.001%
Sulfate (SO_4)	0.004%

500	ml	2.90
2.5	Lt.	13.00

T 81972 Formic acid 90% Lab-Grade

CAS 64-18-6
UN-1779 IMDG - 8/II
HCOOH 33.0% F.W.46.03

500	ml	4.35

T 81977 Formic acid 90% ACS/AR

CAS 64-18-6
UN-1779 IMDG - 8/II
HCOOH 88.0% F.W.46.03
Dilution Test Passes test

Maximum Limits

Color (APHA)	15
Residue after Evaporation	0.002%
Acetic acid (CH_3COOH)	0.4%
Ammonium (NH_4)	0.005%
Chloride (Cl)	0.001%
Sulfate (SO_4)	0.002%
Sulfite (SO_3)	Passes test
Heavy Metals (as Pb)	5 ppm
Iron (Fe)	5 ppm

500	ml	5.40
6x500	ml	27.00

T 81974 Formic acid 98-100%Lab-Grade

CAS 64-18-6
HCOOH
UN-1779 IMDG - 8/II

500	ml	8.85
2.5	lt	39.50

T 82500 d- Fructose Lab-Grade

CAS 57-48-7
$C_6H_{12}O_6$

Specific rotation (a)^{20}D	-92 to - 88 deg
Lead	0.0002%

500	gm	9.25

T 82505 d-Fructose ACS/AR for biochemistry & microbiology

CAS 57-48-7
$C_6H_{12}O_6$ F.W.180.16

Acidity	To pass test
Color of solution	To pass test

Maximum Limits

Glucose	0.2%
Loss on drying	0.5%
Residue on Ignition	0.5%
Chloride (Cl)	0.018%
Sulfate (SO_4)	0.025%
Arsenic (As)	0.0001%
Calcium and Magnesium (as Ca)	0.005%
Heavy Metals (as Pb)	0.0005%
Hydroxymethylfurfural	To pass test

250	gm	9.10

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 82600 Gentian Violet 2% (Aqueous)

500	ml	5.25

T 83359 Gibberelic acid Lab-Grade

CAS 77-06-5
$C_{19}H_{22}O_6$ 90% F.W.346.38

1	gm	3.40

T 83945 Glycerin Lab-Grade

CAS 56-81-5
$C_3H_5(OH)_3$ 98% F.W.92.10

500	ml	5.10
2.5	lt	23.40

T 83950 Glycerin ACS/AR

CAS 56-81-5
$C_3H_5(OH)_3$ 99.5% F.W 92.10

Neutrality	Passes test
Maximum Limits	
Color (APHA)	10
Residue after Ignition	0.005%
Chlorinated compounds (as Cl)	0.003%
Sulfate (SO_4)	0.001%
Acrolein, Glucose and Ammonium compounds	Passes test
Fatty acid esters (as Butyric acid)	0.05%
Silver reducing substances	Passes test
Substances darkened by sulfuric acid	Passes test
Heavy Metals (as Pb)	2 ppm
Water (H_2O)	0.5%

500	ml	6.00
6x500	ml	30.00
2.5	lt	28.00

T 84357 Glycine Lab-Grade

CAS 56-40-6
$C_2H_5NO_2$ 98.5% F.W.75.07

500	gm	10.50
6x500	gm	52.50

T 84362 Glycine ACS/AR

CAS 56-40-6
$C_2H_5NO_2$ 98.5% F.W.75.07

Maximum Limits	
Residue after Ignition	0.1%
Heavy metals (as Pb)	0.002%
Chloride (Cl)	0.005%
Sulphate (SO_4)	0.005%
Ammonium (NH_4)	0.005%
Substances darkened by sulfuric acid	Passes test
Hydrolyzable substances	Passes test

100	gm	4.25

T 84401 Gram's Stain No. 1 (Crystal Violet)

125	ml	1.10
4x125	ml	3.30

T 84501 Gram's Stain No. 2 (Gram's Iodine)

125	ml	1.25
4x125	ml	3.75

T 84601 Gram's Stain No. 3 (Acetone Alcohol)

125	ml	1.50
4x125	ml	4.50

T 84701 Gram's Stain No. 4 (Safranine 'O').

125	ml	1.50
4x125	ml	4.50

T 88700 Hematoxylin stain solution (Delafield)

125	ml	3.10
4x125	ml	9.30

T 88705 Hematoxylin stain solution (Ehrlich)

125	ml	3.60
4x125	ml	10.80

T 88710 Hematoxylin stain solution (Harris)

125	ml	3.60
4x125	ml	10.80

T 88893 Hexane 65-70 C Fraction from petroleum Lab-Grade

CAS 110-54-3
UN - 1208 IMDG - 3/1/II
$CH_3(CH_2)_4CH_3$

500	ml	1.50
6x500	ml	7.50
2.5	lt	7.00

T 88898 Hexane 65-70 C Fraction from petroleum ACS/AR

CAS 110-54-3
UN - 1208 IMDG - 3.1/II
$CH_3(CH_2)_4CH_3$

Maximum Limits	
Color (APHA)	10
Residue after Evaporation	0.001%
Water soluble Titrable acid	0.0003 meq/g
Sulfur compounds (as S)	0.005%
Thiophene	Passes test

500	ml	2.40
6x500	ml	12.00
2.5	lt	11.25

T 88913 Hexane fraction from petroleum for HPLC

CAS 110-54-3
UN - 1208 IMDG - 3.1/II
$CH_3(CH_2)_4CH_3$

Maximum Limits	
Color (APHA)	10
Residue after Evaporation	2 ppm
Titrable acid (H_2O soluble)	0.03 µeq/g
Sulfur compounds (as S)	0.005%
Thiophene	To pass test
Water (H_2O)	0.01%

1	lt	9.25
6x1	lt	46.25

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 90054 Hydrazine Hydrate 99% ACS/AR

CAS 7803-57-8
UN - 2030 IMDG - 8/II
$NH_2NH_2H_2O$ 85% F.W.50.06

500	ml	9.70
6x500	ml	48.50

T90063 Hydrazine Hydrochloride Lab-Grade

CAS 5341-61-7
NH_2NH_2HCl 98% F.W.104.98

100	gm	4.25
6x100	gm	21.25

T 90084 Hydrazine Sulfate Lab-Grade

CAS 10034-93-2
$NH_2NH_2H_2SO_4$ 99% F.W.130.12

100	gm	1.40
500	gm	5.60

T 90089 Hydrazine Sulfate ACS/AR

CAS 10034-93-2
$NH_2NH_2H_2SO_4$ 99.5% F.W.130.12

Maximum Limits	
Insoluble matter	0.005%
Residue after Evaporation	0.05%
Chloride (Cl)	0.005%
Heavy metals (as Pb)	0.002%
Iron (Fe)	0.001%

100	gm	2.40
500	gm	9.60
6x500	gm	48.00

T 90312 Hydrobromic acid abt 48% Hbr ACS/AR

CAS 10035-10-6
UN-1788 IMDG - 8/II
HBr 48-49% F.W.80.91

Maximum Limits	
Residue after Ignition	0.002%
Chloride (Cl)	0.05%
Iodide (I)	0.003%
Phosphate (PO_4)	0.001%
Sulfate and Sulfite (as SO_4)	0.003%
Heavy metals as (as Pb)	5 ppm
Iron (Fe)	1 ppm
Selenium (Se)	0.01 ppm

500	ml	7.80
6x500	ml	39.00

T 90239 Hydrochloric acid 35-38% Lab-Grade

CAS 7647-01-0
UN-1789 IMDG - 8/11
HCl 36.5-38% F.W.36.46

Specific gravity	Passes test
Maximum Limits	
Heavy metals (as Pb)	0.0001%
Iron (Fe)	0.0005%
Nonvolatile Residue	0.5%
Oxidizing substances (as Cl_2)	0.003%
Reducing substances (as SO_3)	0.007%
Sulfate (SO_4)	0.5%
Organic compounds	Passes test

2x500	ml	4.10
8x500	ml	14.40
2.5	lt	5.70
4x2.5	lt	18.00
5	lt	8.40

T 90244 Hydrochloric acid 35.4% ACS/AR

CAS 7647-01-0
UN-1789 IMDG - 8/II
HCl 36.5-38% F.W.36.46

Maximum Limits	
Color (APHA)	10
Residue after ignition	5 ppm
Bromide (Br)	0.005%
Sulfate (SO_4)	1 ppm
Sulfite (SO_3)	1 ppm
Extractable organic substances	5 ppm
Free Chlorine (Cl)	1 ppm
Ammonium (NH_4)	3 ppm
Arsenic (As)	0.01 ppm
Heavy metals (as Pb)	1 ppm
Iron (Fe)	0.2 ppm

2x500	ml	4.30
8x500	ml	15.10
2.5	lt	7.00
4x2.5	lt	24.00

T 90301 Hydrochloric Acid solution 5%

125	ml	0.40
4x125	ml	1.20

T 90378 Hydrogen Peroxide 30% 100 vol. Lab-Grade

CAS 7722-84-1
UN - 2014 IMDG - 5.1/II
H_2O_2 29-32% F.W.34.01

500	ml	2.70
6x500	ml	13.50

T 90383 Hydrogen Peroxide 30% 100 vol. ACS/AR

CAS 7722-84-1
UN -2014 IMDG - 5.1/II
H_2O_2 29-32% F.W.34.01

Maximum Limits	
Color (APHA)	10
Residue after evaporation	0.002%
Titrable acid	0.0006 meq/g
Chloride (Cl)	3 ppm
Nitrate (NO_3)	2 ppm
Phosphate (PO_4)	2 ppm
Sulfate (SO_4)	5 ppm
Ammonium (NH_4)	5 ppm
Heavy metal (as Pb)	1 ppm
Iron (Fe)	0.5 ppm

500	ml	3.25
6x500	ml	16.25

T 94359 8-Hydroxyquinoline ACS/AR

CAS 148-24-3
HOC_9H_6N 99-101% F.W.145.16

Melting point	72.5°-74.0°C
Suitability for Magnesium Determination	Passes test
Maximum Limits	
Insoluble in Alcohol	0.05%
Residue after Ignition	0.05%
Sulfate (SO_4)	Passes test

100	gm	8.80
500	gm	39.00

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 94501 Indigo Carmine ACS/AR

10	gm	1.50
25	gm	3.25

T 94601 3-Indole acetic acid Lab-Grade

CAS 87-51-4

$C_{10}H_9NO_2$ F.W. 175.19

Assay (acidimetric) min. 96%

1	gm	2.30
5	gm	9.25

T 94651 Iodine Solution Lugol's

125	ml	1.80
4x125	ml	5.40

T 95651 Iodine 0.1 N Solution

500	ml	3.50

T 95667 Iodine Resublimed ACS/AR

CAS 7553-56-2

I_2 99.8% F.W.253.81

Maximum Limits

Nonvolatile matter	0.01%
Chlorine and bromine (as Cl)	0.005%

100	gm	8.50
6x100	gm	42.50
500	gm	41.40
6x500	gm	207.00

T 97523 Karl Fischer Reagent A&B set (Pyridine Free) Lab-Grade

for moisture determination

500	ml	17.00
6x500	ml	85.00

T 97526 Karl Fischer Reagent Composit single solution (Pyridine Free) Lab-Grade

500	ml	17.00
6x500	ml	85.00

T 99040 Lactic acid Lab-Grade

CAS 50-21-5

$CH_3CHOHCOOH$ 85-90%

500	ml	8.00

T 99045 Lactic acid ACS/AR

CAS 50-21-5

$CH_3CHOHCOOH$ 85-90%

Substances darkened by sulfuric acid	Passes test

Maximum Limits

Residue after ignition	0.02%
Chloride (Cl)	0.001%
Sulfate (SO_4)	0.002%
Heavy metals (as Pb)	5 ppm
Iron (Fe)	5 ppm

500	ml	10.70
6x500	ml	53.50

T 99150 Lactose Monohydrate ACS/AR

for Bacteriological purpose

CAS 5989-81-1

$C_{12}H_{22}O_{11}.H_2O$ F.W.360.32

Water (H_2O) 4-6%

Maximum Limits

Insoluble matter	0.005%
Residue after ignition	0.03%
Dextrose	Passes test
Sucrose	Passes test
Heavy metals (as Pb)	5 ppm
Iron (Fe)	5 ppm

500	gm	4.80
6x500	gm	24.00

T 99201 Lead Metal shots Lab-Grade

CAS 7439-92-1

Pb F.W 207.19

500	gm	6.80

T 99206 Lead Metal granular Lab-Grade

CAS 7439-92-1

Pb F.W 207.19

125	gm	2.85
4X125	gm	8.50

T 99296 Lead (II) Acetate trihydrate ACS/AR

CAS 6080-56-4

UN -1616 IMDG - 6.1/III

$(CH_3COO)_2Pb.3H_2O$ 99-103% F.W.379.33

Maximum Limits

Insoluble matter	0.01%
Chloride (Cl)	5 ppm
Nitrate and Nitrite (as NO_3)	0.005%
Copper (Cu)	0.002%
Substances not precipitated by hydrogen sulfide (as sulfates)	0.05%
Iron (Fe)	0.001%

500	gm	4.40
6x500	gm	

T 99440 Lead (II) Acetate Basic anhydrous for sugar analysis according to horne Lab-Grade

CAS -51404-69-4

UN-1616 IMDG - 6.1/III

$(CH_3COO)_2Pb.Pb(OH)_2$ 72-74% F.W.566.5

1	kg	7.00
2.5	kg	15.00

T 99400 Lead (II) Carbonate basic Lab-Grade

CAS 1319-46-6

$(PbCO_3)_2.Pb(OH_2)$ F.W.775.60

500	gm	10.50

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 99445 Lead (II) Carbonate basic ACS/AR

CAS 1319-46-6
$(PbCO_3)_2.Pb(OH_2)$ F.W.775.60

Maximum Limits

Insoluble in dilute acetic acid	0.02%
Chloride (Cl)	0.002%
Nitrate and nitrite (as NO_3)	Passes test (limit about 0.005%)
Substances not precipitated by hydrogen sulfide (as sulfates)	0.2%
Cadmium (Cd)	0.002%
Iron (Fe)	0.005%
Zinc (Zn)	0.003%

500	gm	145.00

T 99412 Lead (II) Chloride Anhydrous Lab-Grade

CAS 7758-95-4
$PbCl_2$ 97% F.W.278.10

500	gm	11.10

T 99445 Lead (II) Chromate

CAS 7758-97-6
$PbCrO_4$ 98% F.W.323.21

500	gm	10.50

T 99536 Lead Dioxide Lab-Grade

CAS 1309-60-0
UN - 1872 IMDG - 5.1/III
PbO_2 94% F.W.239.20

500	gm	5.40

T 99756 Lead (II) Nitrate Lab-Grade

CAS 10099-74-8
UN-1469 IMDG - 5.1/II
$Pb(NO_3)_2$ 99% F.W.331.21

500	gm	3.00

T 99761 Lead (II) Nitrate ACS/AR

CAS 10099-74-8
UN-1469 IMDG - 5.1/II
$Pb(NO_3)_2$ 99.5% F.W.331.21

500	gm	6.00
6x500	gm	30.00

T 99812 Lead Oxide red Lab-Grade

CAS 1314-41-6
Pb_3O_4 85% F.W.685.60

500	gm	3.40

T 99817 Lead (II) Oxide yellow Lab-Grade

CAS 1317-36-8
PbO 98% F.W.223.20

500	gm	3.10
6x500	gm	15.50

T 99983 Lead (II) Sulfate Lab-Grade

CAS 7446-14-2
$PbSO_4$ 97% F.W.303.25

500	gm	11.10

T 100600 Leishman's stain solution for blood smears

125	ml	1.00
4x125	ml	3.00

T 100610 Light Green stain solution

125	ml	1.25
4x125	ml	3.75

T 100625 Litmus Blue indicator paper

one pkt contains 100 leaves

1	pkt	1.60
24	pkt	29.00

T 100630 Litmus Red indicator paper

one pkt contains 100 leaves

1	pkt	1.60
24	pkt	29.00

T 100635 Litmus Blue indicator solution

highly concentrated solution

125	ml	1.00
4x125	ml	3.00

T 100640 Litmus Red indicator solution

highly concentrated solution

125	ml	1.00
4x125	ml	3.00

T 100712 Lithium Bromide anhydrous Lab-Grade

CAS 7550-35-8
LiBr 98% F.W.86.85

500	gm	27.10

T 101262 Litmus pH indicator Lab-Grade

CAS 1393-92-6
approx. F.W.3300

25	gm	6.25
100	gm	19.00

T 103010 Magnesium metal ribbon Lab-Grade

CAS 7439-95-4
Mg 99.7% F.W.24.31

25	gm	1.65
6x25	gm	8.00

T 103021 Magnesium Carbonate Lab-Grade

CAS 39409-82-0

Soluble mater	1.0%
Chloride	0.05%
Calcium	1%
Iron	0.04%

125	gm	1.25
500	gm	3.80

T 103026 Magnesium Carbonate ACS/AR

100	gm	4.80
500	gm	19.00

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 103139 Magnesium chloride hexahydrate Lab-Grade

CAS 7791-18-6
$MgCl_2.6H_2O$ F.W.203.30

Assay (ex Cl)	Min. 89%
Iron	0.002%
Phosphate	0.004%

500 gm 1.50

T 103144 Magnesium chloride hexahydrate ACS/AR

CAS 7791-18-6
$MgCl_2.6H_2O$ 99-102% F.W.203.30

Maximum Limits	
Insoluble matter	0.005%
Nitrate (NO_3)	0.001%
Phosphate (PO_4)	5 ppm
Sulfate (SO_4)	0.002%
Ammonium (NH_4)	0.002%
Barium (Ba)	0.005%
Calcium (Ca)	0.01%
Heavy metal (as Pb)	5 ppm
Iron (Fe)	5 ppm
Manganese (Mn)	5 ppm
Potassium (K)	0.005%
Sodium (Na)	0.005%
Strontium (Sr)	0.005%

500 gm 1.55
6x500 gm 7.75

T 103442 Magnesium nitrate hexahydrate ACS/AR

CAS 13446-18-9
$Mg(NO_3)_2.6H_2O$ 99-102% F.W.256.41

pH of a 5% solution at 25°C	5.0-8.2
Maximum Limits	
Insoluble matter	0.005%
Chloride (Cl)	0.001%
Phosphate (PO_4)	5 ppm
Sulfate (SO_4)	0.005%
Ammonium (NH_4)	0.003%
Barium (Ba)	0.005%
Calcium (Ca)	0.01%
Heavy metal (as Pb)	5 ppm
Iron (Fe)	5 ppm
Manganese (Mn)	5 ppm
Potassium (K)	0.005%
Sodium (Na)	0.005%
Strontium (Sr)	0.005%

500 gm 5.50
6x500 gm 27.50

T 103713 Magnesium sulfate heptahydrate ACS/AR

CAS 10034-99-8
$MgSO_4.7H_2O$ 98.0-102.0% F.W.246.48

pH of a 5% solution at 25°C	5.0-8.2
Maximum Limits	
Insoluble matter	0.005%
Chloride (Cl)	5 ppm
Nitrate (NO_3)	0.002%
Ammonium (NH_4)	0.002%
Arsenic (As)	2 ppm
Calcium (Ca)	0.02%
Heavy metal (as Pb)	5 ppm
Iron (Fe)	5 ppm
Manganese (Mn)	5 ppm
Potassium (K)	0.005%
Sodium (Na)	0.005%
Strontium (Sr)	0.005%

500 gm 3.00
6x500 gm 15.00

T 104216 Manganese (II) Acetate Tetrahydrate ACS/AR

CAS 6156-78-1
$(CH_3COO)_2Mn.4H_2O$ 99% F.W.245.09

Maximum Limits	
Chloride (Cl)	0.003%
Heavy metal (as Pb)	0.001%
Insoluble matter	0.01%
Iron (Fe)	0.001%
Sulfate (SO_4)	0.005%

500 gm 4.30

T 104272 Manganese (II) chloride Tetrahydrate ACS/AR

CAS 13446-34-9
$MnCl_2.4H_2O$ 98-101% F.W.197.90

pH of a 5% solution at 25°C	3.5-6.0
Maximum Limits	
Insoluble matter	0.005%
Sulfate (SO_4)	0.005%
Calcium (Ca)	0.005%
Heavy metals (as Pb)	5 ppm
Iron (Fe)	5 ppm
Magnesium (Mg)	0.005%
Potassium (K)	0.01%
Sodium (Na)	0.05%
Zinc (Zn)	0.005%

500 gm 3.45
6x500 gm 17.25

T 104070 Manganese dioxide tech 85% Lab-Grade

CAS 1313-13-9
MnO_2 80% F.W.86.94

500 gm 1.20

T 104517 Manganese (II) Sulfate monohydrate ACS/AR

CAS 10034-96-5
$MnSO_4.H_2O$ 98-101% F.W.169.02

Loss on ignition	10-12%
Substances reducing permanganate	Passes test
Maximum Limits	
Insoluble matter	0.01%
Chloride (Cl)	0.005%
Calcium (Ca)	0.005%
Heavy metal (as Pb)	0.002%
Iron (Fe)	0.002%
Magnesium (Mg)	0.005%
Nickel (Ni)	0.02%
Potassium (K)	0.01%
Sodium (Na)	0.05%
Zinc (Zn)	0.005%

500 gm 7.00
6x500 gm 35.00

T 104601 Maleic Acid Lab-Grade

CAS 110-16-7 F.W.116.07

HOOC.CH:CH.COOH

Assay (acidimetric)	99.5 to 100.5%
M.P.	136-141 deg C

250 gm 2.20

(INTERNATIONAL PRICE LIST IN U.S. DOLLARS)

T. BAKER LAB CHEMICALS

T104651 D (-) Mannitol ACS/AR

CAS 69-65-8
M.W. 182. 17
$C_6H_{14}O_6$

Specific rotation (a)^{20}D		+140 to +143 deg
Assay		Min. 99%
Acidity (CH3COOH)		0.005%
Chloride		0.001%
Iron		0.0005%
reducing sugars (glucose)		0.05%
500	gm	15.75

T104695 Menthol crystals Lab-Grade

CAS 2216-51-5
$C_{10}H_{20}O$ F.W.156.27

100	gm	18.60

T105319 Mercuric acetate Lab-Grade

CAS 1600-27-7
UN - 1624 IMDG 6.1/II
$(C_2H_3O_2)_2Hg$ F.W.156.27

100	gm	12.00

T105353 Mercuric chloride Lab-Grade

CAS 7487-94-7
UN - 1624 IMDG. 6.1/II
$HgCl_2$ 98% F.W.271.50

250	gm	7.15

T105358 Mercuric chloride ACS/AR

CAS 7487-94-7
UN - 1624 IMDG - 6.1/II
$HgCl_2$ 99.5% F.W.271.50
Soluble in ethyl ether Passes test
Maximum Limits

Residue after reduction	0.02%
Iron (Fe)	0.002%

100	gm	4.95
250	gm	11.15

T105449 Mercuric Iodide red ACS/AR

CAS 7774-29-0
HgI_2 99% F.W.454.40
Solubility in potassium iodide solution Passes test
Maximum Limits

Mercurous mercury (as Hg)	0.1%
Soluble mercury salts (as Hg)	0.05%

100	gm	16.50
500	gm	66.00
6x500	gm	330.00

T105463 Mercuric Nitrate Lab-grade

CAS 7783-34-8
UN- 1625 IMDG 6.1/II
$Hg(NO_3)_2.H_2O$ 58-62% F.W.342.62

100	gm	5.45
500	gm	22.00

T105468 Mercuric Nitrate ACS/AR

CAS 7783-34-8
UN - 1625 IMDG - 6.1/II
$Hg(NO_3)_2.H_2O$ 98% F.W.342.62
Maximum Limits

Residue after reduction	0.01%
Chloride (Cl)	0.002%
Sulfate (SO_4)	0.002%
Iron (Fe)	0.001%
Mercurous mercury (as Hg)	0.2%

100	gm	22.00
500	gm	88.00

T105490 Mercuric Oxide red ACS/AR

CAS 21908-53-2
UN - 1641 IMDG - 6.1/II
HgO 99% F.W.216.59
Maximum Limits

Insoluble in dilute hydrochloric acid	0.03%
Residue after reduction	0.025%
Chloride (Cl)	0.025%
Sulfate (SO_4)	0.015%
Nitrogen compounds (as N)	0.005%
Iron (Fe)	0.005%

100	gm	16.50
500	gm	66.00

T105505 Mercuric Oxide yellow ACS/AR

CAS 21908-53-2
UN-1641 IMDG -6.1/II
HgO 99% F.W.216.59
Maximum Limits

Insoluble in dilute hydrochloric acid	0.03%
Residue after reduction	0.05%
Chloride (Cl)	0.025%
Sulfate (SO_4)	0.01%
Nitrogen compounds (as N)	0.005%
Iron (Fe)	0.003%

100	gm	20.50
500	gm	82.00

T105526 Mercuric Sulfate Lab-Grade

CAS 7783-35-9
UN-1645 IMDG - 6.1/II
$HgSO_4$ 99% F.W.296.65

250	gm	11.15

T105531 Mercuric Sulfate ACS/AR

CAS 7783-35-9
UN-1645 IMDG - 6.1/II
$HgSO_4$ 98% F.W.296.65
Maximum Limits

Residue after reduction	0.02%
Chloride (Cl)	0.003%
Nitrate (NO_3)	Passes test (limit about 0.005%)
Iron (Fe)	0.005%
Mercurous mercury (as Hg)	0.15%

250	gm	55.00

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T105678 Mercurous Nitrate Lab-Grade

CAS 14836-60-3
UN-1627 IMDG - 6.1/II
$Hg_2(NO_3)_2.xH_2O$ 99% F.W.561.22

100	gm	7.50

T 105683 Mercurous Nitrate ACS/AR

0-3
UN-1645 IMDG -6.1/II
$Hg_2(NO_3)_2.2H_2O$ 98% F.W.561.22

Maximum Limits

Insoluble matter	0.005%
Residue after reduction	0.01%
Chloride (Cl)	0.005%
Sulfate (SO_4)	0.005%
Iron (Fe)	0.001%
Mercuric mercury (as Hg)	0.5%

100	gm	22.00
500	gm	88.00

T 107726 Methanol (Methyl Alcohol) Lab-Grade

CAS 67-56-1
UN-1230 IMDG-3.2/II
CH_3OH 99% F.W.32.04

500	ml	1.50
6x500	ml	7.50
1	lt	2.55
2.5	lt	5.15

T 107731 Methanol ACS/AR

CAS 67-56-1
UN-1230 IMDG - 3.1/II
CH_3OH 99.8% F.W.32.04

Appearance	Clear
Substances darkened by sulfuric acid	Passes test
Substances reducing permanganate	Passes test
Maximum Limits	
Color (APHA)	10
Water (H_2O)	0.1%
Residue after evaporation	0.001%
Solubility in water	Passes test
Carbonyl compounds	0.001% each of acetone, formaldehyde, and acetaldehyde
Titrable acid	0.0003 meq/g
Titrable base	0.0002 meq/g

500	ml	1.90
6x500	ml	9.50
1	lt	3.55
6x1	lt	17.75
2.5	lt	7.45

T107618 Methyl acetate Lab-Grade

CAS 79-20-9
UN-1231 IMDG - 3.2/II
CH_3COOCH_3 90% F.W.74.08

500	ml	6.45

T108273 Methyl benzoate Lab-Grade

CAS 93-58-3
$C_6H_5COOCH_3$ F.W.136.14

500	ml	12.50

T109587 Methylene blue for microsocopy Lab-Grade

CAS 26283-09-0 (C.I. 52015)
$C_{16}H_{18}N_3SCl.3H_2O$ F.W.319.86

25	gm	1.90
100	gm	5.15

T109592 Methylene blue Loffler solution

125	ml	1.30
4x125	ml	3.90

T109600 Methyl Orange solution pH 2.9-4.6 orange to yellow

125	ml	1.05
4x125	ml	3.15

T109605 Methyl Red indicator solution

125	ml	1.05
4x125	ml	3.15

T 109610 Methyl Red Stain powder Lab-Grade

C.I. NO. 13020
CAS 493-52-7
M.W. 269.31
$C_{15}H_{15}N_3O_2$
pH transition range:
pH 4.5 - 6.2 red-violet to brownsih yellow
Absorption max:
pH 4.5 523 - 526 nm
pH 6.2 430 - 434 nm

25	gm	2.60

T 109630 Methyl Violet indicator solution

125	ml	1.15
4x125	ml	3.45

T 52297 Methylene Chloride Lab-Grade

CAS 75-09-2
UN-1593 IMDG - 6.1/III
CH_2Cl_2 99% F.W.84.93

500	ml	3.30
2.5	lt	15.30

T 52302 Methylene Chloride ACS/AR

CAS 75-09-2
UN - 1593 IMDG - 6.1/III
CH_2Cl_2 99.5% F.W.84.93

Appearance	Clear
Maximum Limits	
Color (APHA)	10
Residue after evaporation	0.002%
Titrable acid	0.0003 meq/g
Water (H_2O)	0.02%
Free Halogens	Passes test

500	ml	4.30
2.5	lt	19.90

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 24470 Methyl Ethyl Ketone Lab-Grade

CAS 78-93-3
UN - 1193 IMDG - 3.2/II
$C_2H_5COCH_3$ 99% F.W.72.11

500	ml	3.00
6x500	ml	15.00
2.5	lt	14.15

T24475 Methyl Ethyl Ketone ACS/AR

CAS 78-93-3
UN-1193 IMDG - 3.2/II
$C_2H_5COCH_3$ 99% F.W.72.11

Maximum Limits

Color (APHA)	15
Residue after evaporation	0.0025%
Titrable acid	0.0005 meq/g
Water	0.20%

500	ml	4.90
6x500	ml	24.50

T111773 Methyl Orange pH indicator ACS/AR

CAS 547-58-0 (C.I.13025)
$C_{14}H_{14}N_3NaO_3S$ F.W.327.33

Clarity of Solution	Passes test
Visual Transition interval	pH 3.2 to 4.4 (red to yellow)

25	gm	1.50
6x25	gm	7.50

T113072 Methyl Salicylate Lab-Grade

CAS 119-36-8
$C_8H_8O_3$ 98-100.5% F.W.152.15

Solubility in 70% alcohol	Passes test
Specific gravity @25°/25°C	1.180-1.185
Refractive Index @20°C	1.535-1.538
Angular Rotation	Optically inactive

Maximum Limits

Heavy metals (as Pb)	0.004%
Organic volatile impurities	Passes test

500	ml	5.70

T 113101 Murexide indicator powder Lab-Grade

(Ammonium Purpurate)
C.I. 56085.
CAS 3051-09-0
F.W. 284.19
$C_8H_8N_8O_6$

Dye Content	~ 70%
Abs. max (water)	520 nm

1	gm	0.90
5	gm	3.75

T113085 Million's Reagent solution

Reagent for protein test

125	ml	2.00
4x125	ml	8.00

T115351 Naphthalene flakes Lab-Grade

CAS 91-20-3
F.W. 128.17
$C_{10}H_8$

Assay (GC)	Min. 99%
M.P.	79-82 deg C

500	gm	2.35

T115364 a-Naphthol Lab-Grade

CAS 90-15-3
$C_{10}H_7OH$
F.W. 144.17

Assay	Min. 99%
M.P.	94-96 deg C

100	gm	4.50

T135371 b-Naphthol powder Lab-Grade

CAS 135-19-3-
F.W.144.17
$C_{10}H_7OH$

Assay	min. 98%
M.P.	121-123 deg C
1-Naphthol	0.5%

500	gm	5.75

T116618 Neutral red pH indicator ACS/AR

CAS 553-24-2 [C.I.50040]
$C_{15}H_{17}ClN_4$ F.W.288.78

10	gm	4.45
25	gm	8.90

T116701 Nickel Ammonium Sulfate Lab-Grade

CAS 7785-20-8
F.W.394.97
$(NH_4)_2Ni(SO_4)_2.6H_2O$

Assay	min 98.5%
Chloride	0.003%

500	gm	11.00

T116717 Nickel (II) carbonate extra pure Lab-Grade

CAS 12607-70-4
$NiCO_3.2Ni(OH)_2.4H_2O$ 45% F.W.376.24

Maximum Limits

Chloride (Cl)	0.005%
Iron (Fe)	0.005%
Sulfate (SO_4)	0.3%
Lead (Pb)	0.04%
Sodium (Na)	0.03%
Copper (Cu)	0.005%
Zinc (Zn)	0.06%

500	gm	15.30
6x500	gm	76.50

T116730 Nickel (II) chloride hexahydrate ACS/AR

CAS 7791-20-0
$NiCl_2.6H_2O$ 95% F.W.237.71

500	gm	10.00
6x500	gm	50.00

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T116853 Nickel (II) Nitrate hexahydrate Lab-Grade

CAS 13478-00-7
$Ni(NO_3)_2.6H_2O$
UN - 2725 IMDG - 5.1/III

		F.W.290.79
Assay (ex.Ni)		Min. 98%
Chloride		0.005%
Iron		0.02%
500	gm	9.15

T116858 Nickel (II) nitrate hexahydrate ACS/AR

CAS 13478-00-7
UN-2725 IMDG - 5.1/II
$Ni(NO_3)_2.6H_2O$ 99% F.W.290.79

500	gm	13.15
6x500	gm	65.75

T116981 Nickel (II) sulfate Lab-Grade

CAS 10101-97-0
$NiSO_4.6H_2O$
98.-104%

		F.W.262.85
Assay		98-104%
Chloride		0.01%
Heavy metals (Pb)		0.002%
500	gm	8.00

T116986 Nickel (II) sulfate ACS/AR

CAS 10101-97-0
$NiSO_4.6H_2O$ 98.0-102.0% F.W.262.85
Maximum Limits

Insoluble matter	0.005%
Chloride (Cl)	0.001%
Nitrogen compounds (as N)	0.002%
Calcium (Ca)	0.005%
Cobalt (Co)	0.002%
Copper (Cu)	0.005%
Iron (Fe)	0.001%
Magnesium (mg)	0.005%
Manganese (Mn)	0.002%
Potassium (K)	0.01%
Sodium (Na)	0.05%

500	gm	20.50
6x500	gm	102.50

T117005 Nigrosine Water soluble Lab-Grade

C.I. 50420
CAS 8005-03-6

Abs.max (50% ethanol)	570-580 nm
10 gm	1.00
25 gm	2.00

T117201 Ninhydrin powder ACS/AR

CAS 485 -47-2-

	F.W. 178.14
$C_9H_4O_3H_2O$	
Assay	min. 99%
Sulphated ash	0.1%
5 gm	6.50
10 gm	12.90

T116991 Ninhydrin indicator solution

125	ml	2.75
4x125	ml	8.25

T117318 Nitric acid 69-72% Lab-Grade

CAS 7697-37-2
UN-2031 IMDG - 8/II
HNO_3 68.5-69.5% F.W.63.01

2x500	ml	4.80
8x500	ml	16.50
2.5	lt	6.70
4x2.5	lt	23.00

T117323 Nitric acid 69-72% ACS/AR

CAS 7697-37-2
UN-2031 IMDG - 8/II
HNO_3 69-71% F.W.63.01
Appearance: Colorless and free form suspended matter or sediment.

Maximum Limits

Color (APHA)	10
Residue after ignition	5 ppm
Chloride (Cl)	0.5 ppm
Sulfate (SO_4)	1 ppm
Arsenic (As)	0.01 ppm
Heavy metals (as Pb)	0.2 ppm
Iron (Fe)	0.2 ppm
2x500 ml	5.00
8x500 ml	17.50
2.5 lt	8.25
4x2.5 lt	28.50

T117654 Nitrobenzene Lab-Grade

CAS 98-95-3
UN-1662 IMDG-6.1/II
$C_6H_5NO_2$ 99% F.W.123.11

500	ml	3.20

T117659 Nitrobenzene ACS/AR

CAS 98-95-3
UN-1662 IMDG - 6.1/II
$C_6H_5NO_2$ 99% F.W.123.11
Maximum Limits

Residue after evaporation	0.005%
Water-soluble titrable acid	0.0005 meq/g
Chloride (Cl)	5 ppm
500 ml	6.60

T117701 Oleic Acid Lab-Grade

CAS 112-80-1

	F.W.282-47
$C_{17}H_{33}COOH$	
Assay (GC)	65-70%
Iodine value	85-93
500 ml	2.75

T117905 Orcein Stain powder Lab-Grade

CAS 1400-62-0

1	gm	7.75

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 117675 Orange G Solution (aqueous)

125	ml	2.50
4x125	ml	7.50

T 117690 Orcinol (reagent for sugars) Lab-grade

CAS 6153-39-5

F.W.124.15

$CH_3C_6H_3(OH)_2$

5	gm	12.50
10	gm	22.80

T 122362 Oxalic acid ACS/AR

CAS 6153-56-6

$(COOH)_2.2H_2O$	99.5102.5%	F.W.126.07
Substances darkened by hot sulfuric acid		Passes test
Maximum Limits		
Insoluble matter		0.005%
Residue after ignition		0.01%
Chloride (Cl)		0.002%
Sulfate (SO_4)		0.005%
Calcium (Ca)		0.001%
Nitrogen compounds (as N)		0.001%
Heavy metals (as Pb)		5 ppm
Iron (Fe)		2 ppm

500	gm	3.30
6x500	gm	16.50

T 123050 Mineral oil heavy (Paraffin liquid heavy)

Lab-Grade

CAS 8021-95-11

Viscosity @40°C	Min.34.5 cs
Specific Gravity @25°C	0.845-0.905
Neutrality	Passes test
Maximum Limits	
Readily carbonizable substances	Passes test
Limit of Polynuclear compounds	Passes test
Solid Paraffin	Passes test

1	lt	7.00

T 123053 Mineral oil light (Paraffin liquid light)

Lab-Grade

CAS 8021-95-1

Specific Gravity @ 25°C	0.818-0.880
Neutrality	Passes test
Maximum Limits	
Viscosity @40°C	33.5 cs
Readily carbonisable substances	Passes test
Limit of Polynuclear compounds	Passes test
Solid Paraffin	Passes test

500	ml	2.75
1	lt	5.00
2.5	lt	12.15

T 123261 Paraformaldehyde Lab-Grade

CAS 30525-89-4

UN-2213 IMDG-4.1/III

$(H.CHO)_n$	95%	F.W. 30.03
Formaldehyde content		91.0-93.0%
Maximum Limits		
Acidity (as HCOOH)		0.03%
Ash		0.01%
Iron (Fe)		0.0002%
Water		9.0%

500	gm	3.45

T 123301 Peppermint Oil Lab-Grade

25	gm	3.00

T 123440 Peptone Lab-Grade

Total Nitrogen	14.2 - 15.5%
a-Amini Nitrogen	3.5%

100	gm	3.00

T 124817 Perchloric acid 60% ACS/AR

CAS 7601-90-3

UN-1873 IMDG - 5.1/I

$HClO_4$	60-62%	F.W.100.46
Maximum Limits		
Color (APHA)		10
Residue after ignition		0.003%
Silicate and phosphate (as SiO_2)		5 ppm
Chloride (Cl)		0.001%
Nitrogen compounds (as N)		0.001%
Sulfate (SO_4)		0.001%
Heavy metals (as Pb)		1 ppm
Iron (Fe)		1 ppm

500	ml	12.00
6x500	ml	60.00

T 124820 Perchloric acid 70% ACS /AR

CAS 7601-90-3

UN-1873 IMDG - 5.1/I

$HClO_4$	69-72%	F.W.100.46
Maximum Limits		
Color (APHA)		10
Residue after ignition		0.003%
Silicate and phosphate (as SiO_2)		5 ppm
Chloride (Cl)		0.001%
Nitrogen compounds (as N)		0.001%
Sulfate (SO_4)		0.001%
Heavy metals (as Pb)		1 ppm
Iron (Fe)		1 ppm

500	ml	13.15
6x500	ml	65.75

T 125021 Petroleum ether 40-60°C ACS/AR

CAS 8032-32-4

UN-1268 IMDG - 3.1/II

Boiling range	40°-60°C
Maximum Limits	
Acidity	Passes test
Color (APHA)	10
Residue after evaporation	0.001%

500	ml	4.15
6x500	ml	20.75

T 125028 Petroleum ether 60-80°C ACS/AR

CAS 8032-32-4

UN-1268 IMDG -3.2/II

Boiling range	60°-80°C
Odor	Passes test
Appearance and color	Passes test
Acidity	Passes test
Maximum Limits	
Residue after evaporation	0.001%
Heavy Oils and Fats (Spot test)	Passes test
Sulfur (Doctor test)	Negative

500	ml	2.00
6x500	ml	10.00
2.5	lt	9.00

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 123035 Petroleum ether 80-100°C ACS/AR

CAS 8032-32-4
UN-1268 IMDG -3.3/II
Boiling range 80°-100°C

500	ml	8.25

T 125608 Phenol crystal ACS/AR

CAS 108-95-2
UN - 1671 IMDG - 6.1/II
C_6H_5OH 99% F.W.94.11
Freezing Point (Dry) Min.40.5°C
Clarity of solution Passes test
Maximum Limits
Residue after evaporation 0.05%
Water 0.5%

500	gm	5.15
6x500	gm	25.75

T 125621 Phenolphthalein powder Lab-Grade

CAS-77-09-8
F.W. 318.33
$C_{20}H_{14}O_4$
Assay (dried) min. 98%
pH transition range:
pH 8.2 -9.8 colourless to red violet
Abs. max (pH 9.8) 551-554 nm

125	gm	5.00

T 125626 Phenolphthalein indicator solution 1% alcoholic

125	ml	1.00
4x125	ml	3.00

T 125701 Phenol Red Water Soluble indicator powder Lab-Grade

CAS 143-74-8
F.W. 354.38
$C_{19}H_{14}O_5S$

1	gm	2.00
5	gm	8.00

T 125706 Phenol Red indicator Solution standard

125	ml	0.95
4x125	ml	2.85

T 114120 Phosphomolybdic acid ACS /AR

CAS 51429-74-4
$H_3PO_4.12MoO_3.24H_2O$ 98% F.W.336.74
Maximum Limits
Insoluble matter 0.01%
Chloride (Cl) 0.02%
Sulfate (SO_4) 0.025%
Ammonium (NH_4) 0.01%
Calcium (Ca) 0.02%
Heavy metal (as Pb) 0.005%
Iron (Fe) 0.005%

25	gm	8.00
100	gm	31.45
6x100	gm	157.25

T 114110 Phosphomolybdic Acid Reagent indicator solution

125	ml	1.50
4x125	ml	4.50

T 128540 o-Phosphoric acid Lab-Grade

CAS 7664-38-2
UN - 1805 IMDG - 8/III
H_3PO_4 85% F.W.98.00

500	ml	4.40
6x500	ml	22.00
2.5	lt	20.15

T 128545 o-Phosphoric acid ACS /AR

CAS 7664-38-2
UN - 1805 IMDG - 8/III
H_3PO_4 85.0% F.W.98.00
Maximum Limits
Color (APHA) 10
Insoluble matter, calcium, magnesium and ammonium hydroxide precipitate 0.005%
Chloride (Cl) 3 ppm
Nitrate (NO_3) 5 ppm
Sulfate (SO_4) 0.003%
Volatile acids (as CH_3COOH) 0.001%
Antimony (Sb) 0.002%
Arsenic (As) 1 ppm
Heavy metal (as Pb) 0.001%
Iron (Fe) 0.003%
Manganese (Mn) 0.5 ppm
Potassium (K) 0.005%
Sodium (Na) 0.025%
Reducing substances Passes test

500	ml	5.70
6x500	ml	28.50

T 122270 o-Phosphoric acid for steel industries Lab-Grade

CAS 7664-38-2
UN - 1805 IMDG - 8/III
H_3PO_4 85.0% F.W.98.00

500	ml	6.00

T 128526 Phosphorous oxychloride Lab-Grade

CAS 10025-87-3
UN - 1810 IMDG- 8/II
$POCl_3$ 98-101% F.W.153.33

500	ml	10.00

T 128679 Phosphorous pentoxide ACS /AR

CAS 1314-56-3
P_2O_5 98% F.W.141.94
Maximum Limits
Insoluble matter 0.02%
Phosphorus trioxide (P_2O_3) Passes test (limit about 0.02%)
Ammonium (NH_4) 0.01%
Heavy metal (as Pb) 0.01%

500	gm	12.15

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T162732 Phosphotungstic acid Lab-Grade

CAS 12501-23-4
$H_3PO_4.12WO_3.xH_2O$

Maximum Limits	
Ammonium (NH_4)	0.02%
Chloride (Cl)	0.03%
Heavy metal (as Pb)	0.005%
Insoluble matter	0.02%
Iron (Fe)	0.003%
Nitrate (NO_3)	0.01%
Sulfate (SO_4)	0.02%

100	gm	27.15
6x100	gm	135.75

T162700 Phosphotungstic Acid Reagent indicator solution

125	ml	3.25
4x125	ml	9.75

T128813 Phthalic acid 99.5% ACS /AR

CAS 88-99-3
$C_6H_4(COOH)_2$ 99.5% F.W.166.13

Maximum Limits	
Insoluble matter	0.05%
Residue after ignition (as SO_4)	0.02%
Chloride (Cl)	0.001%
Nitrate (NO_3)	0.005%
Sulfate (SO_4)	0.005%
Heavy metals (as Pb)	0.001%
Iron (Fe)	0.001%
Water (H_2O)	0.5%

500	gm	6.50

T128814 Phthalic anhydride for synthesis Lab-Grade

CAS 85-44-9
UN -2214 IMDG - 8/III
$C_6H_4(CO)_2O$ 99-100.2% F.W.148.12
Appearance White flaky crystals

Maximum Limits	
Melting point	3°C range including 131°C
Residue after ingnition	0.01%
Chloride (Cl)	0.002%
Sulfate (SO_4)	0.003%
Heavy metal (as Pb)	5 ppm
Iron (Fe)	5 ppm

500	gm	3.75
6x500	gm	18.75

T130157 Potassium metal (in liquid paraffin) Lab-Grade

CAS 7440-09-7
UN - 2257 IMDG - 4.3/II
K 98% F.W.39.102

Sodium (Na)	0.75%
Rubidium (Rb)	0.01%
Maximum Limits	
Chloride (Cl)	0.002%
Fluorine (F)	0.15%
Iron (Fe)	0.001%
Sulfur (S)	0.005%

500	gm	240.00

T130174 Potassium acetate ACS /AR

CAS 127-08-2
CH_3COOK 99% F.W.98.14

pH of 5% solution at 25°C	6.5-9.0
Maximum Limits	
Insoluble matter	0.005%
Chloride (Cl)	0.003%
Phosphate (PO_4)	0.001%
Sulfate (SO_4)	0.002%
Calcium, magnesium, and R_2O_3 precipitate	0.01%
Heavy metals (as Pb)	5 ppm
Iron (Fe)	5 ppm
Sodium (Na)	0.03%

500	gm	7.00
6x500	gm	35.00

T130410 Potassium bromate ACS /AR

CAS 7758-01-2
UN-1484 IMDG - 5.1/II
$KBrO_3$ 99.7-100.3% F.W.167

pH of a 5% solution at 25°C	5.0-9.0
Maximum Limits	
Insoluble matter	0.005%
Bromide (Br)	Passes test (limit about 0.005%)
Nitrogen compounds (as N)	0.001%
Sulfate (SO_4)	0.005%
Heavy metal (as Pb)	5 ppm
Iron (Fe)	0.002%
Sodium (Na)	0.01%

500	gm	10.70

T130412 Potassium bromide Lab-Grade

CAS 7758-02-3
KBr 99% F.W.119.00

pH of a 5% solution in water @20°C	5.5-8.5
Maximum Limits	
Chloride (Cl)	0.2%
Iodide (I)	0.001%
Sulfate (SO_4)	0.005%
Bromate (BrO_3)	0.001%
Total Nitrogen (N)	0.005%
Heavy metal (as Pb)	0.0005%
Iron (Fe)	0.0005%
Calcium, Magnesium and R_2O_3	0.005%
Sodium (Na)	0.02%
Insoluble matter	0.005%

500	gm	6.00

T130417 Potassium bromide ACS/AR

CAS 7758-02-3
KBr 99.0% F.W.119.00

pH of a 5% solution at 25°C	5.0 - 8.8
Maximum Limits	
Insoluble matter	0.005%
Bromate (BrO_3)	0.001%
Chloride (Cl)	0.2%
Iodate (IO_3)	0.001%
Iodide (I)	0.001%
Nitrogen compounds (as N)	0.005%
Sulfate (SO_4)	0.005%
Barium (Ba)	0.002%
Calcium, magnesium, and R_2O_3 precipitate	0.005%
Heavy metal (as Pb)	5 ppm
Iron (Fe)	5 ppm
Sodium (Na)	0.02%

500	gm	10.75
6x500	gm	53.75

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 130503 Potassium carbonate anhydrous Lab-Grade

CAS 584-08-7

K_2CO_3	99.0-100.5%	F.W.138.21
Maximum Limits		
Heavy metals (as Pb)		0.002%
Insoluble substances		Passes test
Lead		10 mg/kg
Loss on drying		1%

500	gm	2.80

T 130508 Potassium carbonate anhydrous ACS/AR

CAS 584-08-7

K_2CO_3	99.0%	F.W.138.21
Maximum Limits		
Insoluble matter		0.01%
Chloride (as Cl)		0.003%
Nitrogen compounds (as N)		0.001%
Phosphate (PO_4)		0.001%
Silica (SiO_2)		0.005%
Sulfur compounds (as SO_4)		0.004%
Ammonium hydroxide precipitate		0.01%
Calcium and magnesium precipitate		0.01%
Arsenic (As)		1 ppm
Heavy metal (as Pb)		5 ppm
Iron (Fe)		5 ppm
Sodium (Na)		0.02%

500	gm	4.75

T 130510 Potassium chloride Lab-Grade

CAS 7447-40-7

KCl	99-100.5%	F.W.74.55
Maximum Limits		
Acidity or Alkalinity		Passes test
Loss on drying @105°C		1.0%
Iodide or Bromide		Passes test
Calcium and Magnesium		Passes test
Sodium		Passes test
Heavy metals		0.001%
Organic volatile impurities		Passes test

500	gm	1.80
6x500	gm	9.00

T 130714 Potassium chromate Lab-Grade

CAS 7789-00-6

K_2CrO_4	99%	F.W.194.19

500	gm	5.90
6x500	gm	29.50

T 130719 Potassium chromate ACS/AR

CAS 7789-00-6

K_2CrO_4	99.0%	F.W.194.19
pH of a 5% solution at 25°C		8.6-9.8
Maximum Limits		
Insoluble matter		0.005%
Chloride (Cl)		0.005%
Sulfate (SO_4)		0.03%
Calcium (Ca)		0.005%
Sodium (Na)		0.02%

500	gm	8.15

T 130734 tri-Potassium citrate Lab-Grade

CAS 6100-05-6

$K_3C_6H_5O_7.H_2O$	99.0-100.5%	F.W.324.41
Loss on drying @ 180°C		3.0-6.0%
Alkalinity		Passes test
Maximum Limits		
Tartrate		Passes test
Heavy metals		0.001%
Organic volatile impurities		passes test

500	gm	4.90
6x500	gm	24.50

T 130739 tri-Potassium citrate ACS/AR

CAS 6100-05-6

$K_3C_6H_5O_7.H_2O$	99.0%	F.W.324.41
pH of a 5% solution @ 25°C		8.0-9.0
Maximum Limits		
Ammonium (NH_4)		0.001%
Calcium (Ca)		0.005%
Chloride (Cl)		0.001%
Heavy metal (as Pb)		0.001%
Insoluble matter		0.01%
Iron (Fe)		0.001%

500	gm	6.15
6x500	gm	30.75

T 130802 Potassium dichromate Lab-Grade

CAS 7778-50-9

$K_2Cr_2O_7$	99.0%	F.W.294.18

500	gm	4.90

T 130807 Potassium dichromate ACS/AR

CAS 7778-50-9

$K_2Cr_2O_7$	99.0%	F.W.294.18
Maximum Limits		
Insoluble matter and ammonium hydroxide precipitate		0.005%
Loss on drying		0.05%
Chloride (Cl)		0.001%
Sulfate (SO_4)		0.005%
Calcium (Ca)		0.003%
Sodium (Na)		0.02%

500	gm	5.60

T 131826 Potassium dihydrogen orthophosphate anhydrous Lab-Grade

CAS 7778-77-0

KH_2PO_4	98-100.5%	F.W.136.09
Maximum Limits		
Loss on drying @105°C		1.0%
Insoluble substances		0.2%
Fluoride		0.001%
Arsenic(As)		0.0003%
Heavy metal		0.002%
Lead		0.0005%
Organic volatile impurities		Passes test

500	gm	4.55

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T131831 Potassium dihydrogen orthophosphate anhydrous ACS/AR

CAS 7778-77-0

KH_2PO_4	99%	F.W.136.09
pH of a 5% solution at 25°C		4.1-4.5
Maximum Limits		
Insoluble matter, calcium and ammonnium hydroxide precipitate		0.01%
Loss on drying over sulfuric acid		0.2%
Chloride (Cl)		0.001%
Nitrogen compounds (as N)		0.001%
Sulfate (SO_4)		0.003%
Heavy metals (as Pb)		0.001%
Iron (Fe)		0.002%
Sodium (Na)		0.005%

500	gm	5.90

T131015 Potassium ferrocyanide Lab-Grade

CAS 14459-95-1

$K_4Fe(CN)_6.3H_2O$	98.5-102.0%	F.W.422.39

500	gm	7.00

T131020 Potassium ferrocyanide ACS/AR

CAS 14459-95-1

$K_4Fe(CN)_6.3H_2O$	98.5-102.0%	F.W.422.39
Maximum Limits		
Insoluble matter		0.005%
Chloride (Cl)		0.01%
Sulfate (SO_4)		Passes test (limit about 0.01%)

500	gm	9.00
6x500	gm	45.00

T131031 Potassium fluoride anhydrous Lab-Grade

CAS 7789-23-3
UN-1812 IMDG - 6.1/III

KF	97%	F.W.58.10

500	gm	9.45

T131279 Potassium hydrogen carbonate Lab-Grade

CAS 298-14-6

$KHCO_3$	99.5-101.5%	F.W.100.12
Maximum Limits		
Loss on drying (over silica gel)		0.3%
Normal Carbonate		2.5%
Heavy metal (as Pb)		0.001%
Organic volatile impurities		Passes test

500	gm	5.50

T131348 Potassium hydrogen phthalate Lab-Grade

CAS 877-24-7

$COOHC_6H_4COOK$	99.5%	F.W.204.22

500	gm	5.60

T131353 Potassium hydrogen phthalate ACS/AR

CAS 877-24-7

$COOHC_6H_4COOK$	99.95-100.05%	F.W.204.22
pH of a 0.05m solution at 25.0 ±0.2°C		4.00-4.02
Maximum Limits		
Insoluble matter		0.005%
Chlorine compounds (as Cl)		0.003%
Sulfur compounds (as S)		0.002%
Heavy metal (as Pb)		5 ppm
Iron (Fe)		5 ppm
Sodium (Na)		0.005%

500	gm	8.60
6x500	gm	43.00

T131358 Potassium hydroxide flakes Lab-Grade

CAS 1310-58-3
UN-1813 IMDG - 8/II

KOH	85%	F.W.56.11

500	gm	3.00
5	kg	24.30

T131389 Potassium hydroxide pellets Lab-Grade

CAS 1310-58-3
UN-1813 IMDG - 8/II

KOH	85.0%	F.W.56.11
Maximum Limits		
Insoluble substances		Passes test
Heavy metals		0.003%

500	gm	3.30
6x500	gm	16.50
5	kg	30.00

T131394 Potassium hydroxide pellets ACS/AR

CAS 1310-58-3
UN-1813 IMDG - 8/II

KOH	85.0%	F.W.56.11
Maximum Limits		
Potassium carbonate (K_2CO_3)		2.0%
Chloride (Cl)		0.01%
Nitrogen compounds (as N)		0.001%
Phosphate (PO_4)		5 ppm
Sulfate (SO_4)		0.003%
Ammonium hydroxide precipitate		0.02%
Heavy metal (as Ag)		0.001%
Iron (Fe)		0.001%
Nickel (Ni)		0.001%
Sodium (Na)		0.05%

500	gm	4.60
6x500	gm	23.00
5	kg	41.00

T131487 Potassium iodide Lab-Grade

CAS 7681-11-0

KI	99.0-101.5%	F.W.166.0
Maximum Limits		
Arsenic (As)		0.0003%
Heavy metal (as Pb)		0.001%
Iodate(IO_3)		0.004%
Loss on Drying		1.0%
Nitrate, Nitrite and Ammonia		Passes test
Thiosulfate and Barium		Passes test

250	gm	14.45
500	gm	28.00

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T131492 Potassium iodide ACS/AR

CAS 7681-11-0

KI	99.9%	F.W.166.0
pH of a 5% solution at 25°C		6.0-9.2
Maximum Limits		
Insoluble matter		0.005%
Loss on drying at 150°C		0.2%
Chloride and bromide (as Cl)		0.01%
Iodate (IO_3)		3 ppm
Nitrogen compounds (as N)		0.001%
Phosphate (PO_4)		0.001%
Sulfate (SO_4)		0.005%
Barium (Ba)		0.002%
Calcium , magnesium, and R_2O_3 precipitate		0.005%
Heavy metals (as Pb)		5 ppm
Iron (Fe)		3 ppm
Sodium (Na)		0.005%

100	gm	6.30
250	gm	14.90
6x250	gm	74.50

T131712 Potassium nitrate Lab-Grade

CAS 7757-79-1
UN-1486 IMDG - 5.1/III

KNO_3	99.0-100.5%	F.W.101.10
Maximum Limits		
Chlorate		Passes test
Heavy metal (as Pb)		0.002%
Lead		0.001%
Loss on drying @ 105°C		1%

500	gm	2.20

T131717 Potassium nitrate ACS/AR

CAS 7757-79-1
UN-1486 IMDG-5.1/III

KNO_3	99.0%	F.W.101.10
pH of a 5% solution at 25°C		4.5-8.5
Maximum Limits		
Insoluble matter		0.005%
Chloride (Cl)		0.002%
Iodate (IO_3)		5 ppm
Iodate and nitrite		Passes test (limit about 5ppm IO_3; about 0.001% NO_2)
Phosphate (PO_4)		5 ppm
Sulfate (SO_4)		0.003%
Calcium, magnesium, and R_2O_3 precipitate		0.01%
Heavy metal (as Pb)		5 ppm
Iron (Fe)		3 ppm
Sodium (Na)		0.005%

500	gm	3.30
6x500	gm	16.50

T131828 Potassium oxalate Lab-Grade

CAS 6487-48-5
$(COOK)_2H_2O$

	F.W.184.23
Assay (oxidimetric)	Min. 99%
Chloride	0.005%
Iron	0.005%

500	gm	5.45
6x500	gm	27.25

T131833 Potassium oxalate ACS/AR

CAS 6487-48-5

$(COOK)_2H_2O$	98.5-101.0%	F.W.184.23
Substances darkened by hot sulfuric acid		Passes test
Neutrality		Passes test
Maximum Limits		
Insoluble matter		0.01%
Chloride (Cl)		0.002%
Sulfate (SO_4)		0.01%
Ammonium (NH_4)		0.002%
Heavy metal (as Pb)		0.002%
Iron (Fe)		0.001%
Sodium (Na)		0.02%

500	gm	6.30
6x500	gm	31.50

T131918 Potassium permangante Lab-Grade

CAS 7722-64-7
UN-1490 IMDG - 5.1/II

$KMnO_4$	99.0-100.5%	F.W.158.03
Maximum Limits		
Loss on drying (over silica gel)		0.5%
Insoluble substances		0.2%

500	gm	3.90
6x500	gm	19.50

T131923 Potassium permangante ACS/AR

CAS 7722-64-7
UN-1490 IMDG - 5.1/II

$KMnO_4$	99%	F.W.158.03
Maximum Limits		
Insoluble matter		0.2%
Chloride and chlorate (as Cl)		0.005%
Nitrogen compounds (as N)		0.005%
Sulfate (SO_4)		0.02%

500	gm	7.90
6x500	gm	39.50

T132021 Potassium pyroantimonate ACS/AR

CAS 12208-13-8

$KSb(OH)_6$	94%	F.W.262.90
Maximum Limits		
Water-insoluble matter		0.01%
Sodium (Na)		0.05%

100	gm	13.75
500	gm	55.00

T132223 Potassium sodium (+) tartrate ACS/AR

CAS 6381-59-5

$C_4H_4O_6NaK.4H_2O$	99-102%	F.W.282.22
pH of a 5% solution at 25°C		6.0-8.5
Maximum Limits		
Insoluble matter		0.005%
Chloride (Cl)		0.001%
Phosphate (PO_4)		0.002%
Sulfate (SO_4)		0.005%
Ammonium (NH_4)		0.002%
Calcium (Ca)		0.005%
Heavy metals (as Pb)		5 ppm
Iron (Fe)		0.001%

500	gm	20.90

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T132290 Potassium sulphate ACS/AR

CAS 7778-80-5

K_2SO_4	99%	F.W.174.26
pH of a 5% solution at 25°C		5.5-8.5
Maximum Limits		
Insoluble matter		0.01%
Chloride (Cl)		0.001%
Nitrogen compounds (as N)		5 ppm
Arsenic (As)		2 ppm
Calcium, magnesium, and R_2O_3 precipitate		0.02%
Heavy metal (as Pb)		5 ppm
Iron (Fe)		5 ppm
Sodium (Na)		0.02%

500	gm	2.90

T132392 Potassium thiocyanate ACS/AR

(Pottassium Supho-cynide)

CAS 333-20-0

KSCN	99%	F.W.97.18
Appearance		Colorless or white crystals
pH of a 5% solution at 25°C		5.3-8.7
Maximum Limits		
Insoluble in water		0.005%
Insoluble in alcohol		0.01%
Chloride (Cl)		0.005%
Sulfate (SO_4)		0.005%
Ammonium (NH_4)		0.003%
Heavy metals (as Pb)		5 ppm
Iron (Fe)		2 ppm
Sodium (Na)		0.005%
Iodine-consuming substances		Passes test (Not more than 0.2 ml of 0.1 N iodine solution per gram)

500	gm	16.90
6x500	gm	84.90

T133456 iso-Propyl alcohol Lab-Grade

CAS 67-63-0
UN-1274 IMDG - 3.2/II

$(CH_3)_2CHOH$	99%	F.W.60.10
Specific gravity @25°C		0.783-0.787
Refractive Index @20°C		1.376-1.378
Maximum Limits		
Acidity		Passes test
Nonvolatile residue		0.005%

500	ml	2.15
6x500	ml	10.75
2.5	lt	9.15

T133461 iso-Propyl alcohol ACS/AR

CAS 67-63-0
UN-1274 IMDG - 3.2/II

$(CH_3)_2CHOH$	99.5%	F.W.60.10
Solubility in water		Passes test
Maximum Limits		
Color (APHA)		10
Residue after evaporation		0.001%
Water (H_2O)		0.2%
Titrable acid or base		0.0001 meq/g

500	ml	2.80
6x500	ml	14.00
2.5	lt	11.90

T133476 iso-Propyl alcohol for HPLC

CAS 67-63-0
UN-1274 IMDG - 3.2/II

$(CH_3)_2CHOH$	99.7%	F.W.60.10
Solubility in water		Passes test

Ultraviolet Absorbance (1 cm cell vs. water)

λ(nm)	205	220	230	245	254	280-400
Limit	1.00	0.30	0.15	0.08	0.02	0.01

Maximum Limits	
Color (APHA)	10
Residue after Evaporation	2 ppm
Titrable acid or base	0.1µeq/g
Water (H_2O)	0.05%

500	ml	5.10
1	lt	9.10

T133444 n-Propyl Alcohol Lab-Grade

CAS 71-23-8
$CH_3CH_2CH_2OH$
UN-1274 IMDG -3.2/II

	F.W. 60.10
Assay (GC)	Min 99%
H2O	0.2%
Boiling Range	96-99 deg C 95%)

500	ml	5.75

T133378 Propylene glycol ACS/AR

CAS 57-55-6

$CH_3CH(OH)CH_2OH$	99.5%	F.W.76.10
Maximum Limits		
Color (APHA)		10
Residue after ignition		0.005%
Titrable acid		0.0005 meq/g
Chloride (Cl)		1 ppm
Water (H_2O)		0.2%

500	ml	5.15

T135509 Pyridine Lab-Grade

CAS 110-86-1
UN-1282 IMDG -3.2/II

C_5H_5N	98%	F.W.79.10

500	ml	9.45

T133514 Pyridine ACS/AR

CAS 110-86-1
UN-1282 IMDG - 3.2/II

C_5H_5N	99%	F.W.79.10
Solubility in water		Passes test
Maximum Limits		
Residue after evaporation		0.002%
Water (H_2O)		0.1%
Chloride (Cl)		0.001%
Sulfate (SO_4)		0.001%
Ammonia (NH_3)		0.002%
Copper (Cu)		Passes test (limit abour 5 ppm)
Reducing substances		Passes test

500	ml	12.90
6x500	ml	64.50

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 139210 Resorcinol ACS/AR

CAS 108-46-3
UN-2876 IMDG - 6.1/III

$C_6H_4(OH)_2$	99-100.5%	F.W.110.11
Melting Point		109°-111°C
Solubility		Passes test
Maximum Limit		
Residue after Ignition		0.05%

100	gm	7.40
500	gm	29.50

T 140101 Safranine Lab-Grade

CAS 477-73-6

F.W.350.85

$C_{20}H_{19}N_4Cl$

Dye content (spectro.dried)	~90%
Abs. max (50% ethanol)	530-534 nm

5	gm	1.35
10	gm	2.40

T 142100 Safranine stain indicator solution

125	ml	1.30
4x125	ml	3.90

T 141235 Salicylic Acid Lab-Grade

CAS 69-72-7
$C_6H_4(OH)COOH$

F.W. 138.12

Assay	Min. 99%
M.P.	157-162 deg C

500	gm	4.90

T 142110 Schiff's Reagent solution for detection of Aldehydes

125	ml	3.30
4x125	ml	9.90

T 142120 Selivonaff's Reagent solution

125	ml	1.50
4x125	ml	4.50

T 142130 Semens Diluting Fluid solution

125	ml	1.25
4x125	ml	3.75

T 142230 Silver Nitrate N/10 solution

125	ml	1.80
4x125	ml	5.40

T 142240 Silver Nitrate N/50 solution

125	ml	1.00
4x125	ml	3.00

T 142263 Silver nitrate Lab-Grade

CAS 7761-88-8
UN-1493 IMDG - 5.1/II

$AgNO_3$	99.8%	F.W.169.84

100	gm	37.75
6x100	gm	188.75
500	gm	180.00
6x500	gm	900.00

T 142268 Silver nitrate ACS/AR

CAS 7761-88-8
UN -1493 IMDG - 5.1/II

$AgNO_3$	99%	F.W.169.84
Clarity of solution		Passes test
Maximum Limits		
Chloride (Cl)		5 ppm
Free acid		Passes test
Substances no precipitated by HCl		0.01%
Sulfate (SO_4)		0.002%
Copper (Cu)		2 ppm
Iron (Fe)		2 ppm
Lead (Pb)		0.001%

25	gm	11.45
6x25	gm	57.25
100	gm	40.00
6x100	gm	200.00

T 142392 Silver sulfate Lab-Grade

CAS 10294-26-5

Ag_2SO_4	98%	F.W.311.80

25	gm	12.60

T 142397 Silver sulfate ACS/AR

CAS 10294-26-5

Ag_2SO_4	98%	F.W.311.80
Maximum Limits		
Insoluble matter and silver chloride		0.02%
Nitrate (NO_3)		0.001%
Substance not precipitated by HCl		0.03%
Iron (Fe)		0.001%

25	gm	21.45
6x25	gm	107.25

T 142507 Sodium (metal) in liquid paraffin Lab-Grade

CAS 7440-23-5
UN-1428 IMDG -4.3/I

Na	F.W.22.90
Maximum Limits	
Calcium (Ca)	0.04%
Chloride (as Cl)	0.005%

100	gm	2.40
500	gm	9.30

T 142546 Sodium acetate anhydrous Lab-Grade

CAS 127-09-3
CH_3COONa

F.W.82.03

Assay (non-aqueous)	Min.98%

500	gm	3.60

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 144859 Sodium hydrogen carbonate ACS/AR

(Sodium Bicarbonate)

CAS 144-55-8

$NaHCO_3$ 99.7-100.3% F.W.84.01

Maximum Limits

Insoluble matter	0.015%
Chloride (Cl)	0.003%
Phosphate (PO_4)	0.001%
Sulfur compounds (as SO_4)	0.003%
Ammonium (NH_4)	5 ppm
Calcium, magnesium, and R_2O_3 precipitate	0.02%
Heavy metals (as Pb)	5 ppm
Iron (Fe)	0.001%
Potassium (K)	0.005%

500	gm	3.30
6x500	gm	16.50

T 144949 di-Sodium hydrogen orthophosphate anhydrous Lab-Grade

CAS 7558-79-4

Na_2HPO_4 98-100.5% F.W.141.96

Maximum Limits

Loss on Drying @ 105°C	5.0%
Insoluble substances	0.4%
Chloride (Cl)	0.06%
Sulfate (SO_4)	0.2%
Arsenic (As)	16 ppm
Heavy metals (as Pb)	0.002%

500	gm	4.30

T 144954 di-Sodium hydrogen orthophosphate anhydrous ACS/AR

CAS 7558-79-4

Na_2HPO_4 99% F.W.141.96

pH of a 5% solution at 25°C 8.7-9.3

Maximum Limits

Insoluble matter	0.01%
Loss on drying at 105°C	0.2%
Chloride (Cl)	0.002%
Nitrogen compounds (as N)	0.002%
Sulfate (SO_4)	0.005%
Heavy metals (as Pb)	0.001%
Iron (Fe)	0.002%

500	gm	4.75
6x500	gm	23.75

T 144959 di-Sodium hydrogen orthophosphate dihydrate Lab-Grade

CAS 10028-24-7

$Na_2HPO_4.2H_2O$ 99% F.W.177.99

500	gm	4.00

T 144964 di-Sodium hydrogen orthophosphate dihydrate ACS/AR

CAS 10028-24-7

$Na_2HPO_4.2H_2O$ 99.5% F.W.177.99

pH of a 5% solution in CO_2 free water 9.0-9.2

Maximum Limits

Chloride (Cl)	0.001%
Sulfate (SO_4)	0.005%
Iron (Fe)	0.001%

500	gm	5.60
6x500	gm	28.00

T 144997 Sodium hydrogen sulphate ACS/AR

CAS 7681-38-1

UN-1821 IMDG - 8/III

$NaHSO_4$

Acidity (as H_2SO_4) 39.0-42.0%

Maximum Limits

Insoluble matter and Ammonium hydroxide ppt.	0.01%
Chloride (Cl)	0.001%
Phosphate (PO_4)	0.001%
Calcium and Magnesium Ppt.	0.005%
Heavy metal (as Pb)	5 ppm
Iron (Fe)	0.002%

500	gm	27.50

T 145030 Sodium hydroxide flakes Lab-Grade

CAS 1310-73-2

UN-1823 IMDG - 8/11

NaOH 96% F.W.40.0

500	gm	1.35
1	kg	2.35
5	kg	9.60

T 145035 Sodium hydroxide flakes ACS/AR

CAS 1310-73-2

NaOH F.W.40.0

UN-1823 IMDG - 8/II

Assay	Min. 96%
Chloride	0.1%
Sulphate	0.01%

500	gm	2.20

T 145037 Sodium hydroxide pellets Lab-Grade

CAS 1310-73-2

UN - 1823 IMDG - 8/II

NaOH 97% F.W.40.0

500	gm	1.75
5	kg	14.00

T 145042 Sodium hydroxide pellets ACS/AR

CAS 1310-73-2

UN-1823 IMDG - 8/II

NaOH 98% F.W.40.0

Maximum Limits

Na_2CO_3	1.0%
Chloride (Cl)	0.005%
Nitrogen compounds (as N)	0.001%
Phosphate (PO_4)	0.001%
Sulfate (SO_4)	0.003%
Ammonium hydroxide precipitate	0.02%
Heavy metals (as Ag)	0.002%
Iron (Fe)	0.001%
Mercury (Hg)	0.1 ppm
Nickel (Ni)	0.001%
Potassium (K)	0.02%

500	gm	2.50
5	kg	21.45

T 145372 Sodium hypophosphite Lab-Grade

CAS 10039-56-2

$NaH_2PO_2.H_2O$ 98-101% F.W.105.99

500	gm	11.15

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 145377 Sodium hypophosphite ACS/AR

CAS 10039-56-2
$NaH_2PO_2.H_2O$ 99.0% F.W.105.99

Maximum Limits	
Arsenic (A)	0.0001%
Chloride (Cl)	0.01%
Heavy metal (as Pb)	0.0005%
Insoluble matter	0.01%
Iron (Fe)	0.0005%

500	gm	16.50
6x500	gm	82.50

T 145507 Sodium lauryl sulfate Lab-Grade

CAS 151-21-3
$CH_3(CH_2)_{10}CH_2OSO_3Na$ 99% F.W.288.38

Maximum Limits	
Moisture (KF)	1.0%
Insoluble in water	0.003%
Chloride (Cl)	0.1%
Phosphate (PO_4)	0.0001%

500	gm	6.60

T 145760 Sodium Molybdate Lab-Grade

CAS 10102-40-6
$Na_2MoO_4.2H_2O$
F.W.241.95

Assay (ex Mo)	98-102%
pH (10% soln)	6-10
Chloride	0.02%
Sulphate	0.05%

100	gm	4.00
500	gm	20.00

T 145765 Sodium molybdate ACS/AR

CAS 10102-40-6
$Na_2MoO_4.2H_2O$ 98-102% F.W.241.95

Maximum Limits	
Insoluble matter	0.005%
Chloride (Cl)	0.005%
Phosphate (PO_4)	5 ppm
Sulfate (SO_4)	0.1%
Ammonium (NH_4)	0.001%
Heavy metals (as Pb)	5 ppm
Iron (Fe)	0.001%

100	gm	5.15
500	gm	18.60
6x500	gm	93.00

T146002 Sodium Nitrate Lab-Grade

CAS 7631-99-4
$NaNO_3$
UN -1498 IMDG - 5.1/III
F.W.84.99

Assay (ex NO_3)	Min. 98%
Chloride	0.01%

500	gm	1.95

T146007 Sodium nitrate ACS/AR

CAS 7631-99-4
UN-1498 IMDG - 5.1/III
$NaNO_3$ 99.0% F.W.84.99

Maximum Limits	
Insoluble matter	0.005%
Chloride	0.001%
Iodate (IO_3)	5 ppm
Iodate and nitrite	Passes test (limits about 5 ppm IO_3 about 0.001% NO_2)
Phosphate (PO_4)	5 ppm
Sulfate (SO_4)	0.003%
Calcium , magnesium, and R_2O_3 precipitate	0.005%
Heavy metals (as Pb)	5 ppm
Iron (Fe)	3 ppm

500	gm	2.80
6x500	gm	14.00

T 146015 Sodium Nitrite Lab-Grade

CAS 7632-00-0
F.W. 69.00
UN-1500 IMDG - 5.1/III
$NaNO_2$

Assay (ex NO_2)	min. 98%
Chloride	0.02%
Sulphate	0.03%

500	gm	2.10

T 146020 Sodium nitrite ACSAR

CAS 7632-00-0
UN - 1500 IMDG - 5.1/III
$NaNO_2$ 97.0% F.W.69.00

Maximum Limits	
Insoluble matter	0.01%
Chloride (Cl)	0.005%
Sulfate (SO_4)	0.01%
Calcium (Ca)	0.01%
Heavy metals (as Pb)	0.001%
Iron (Fe)	0.001%
Potassium (K)	0.005%

500	gm	2.35
6x500	gm	11.75

T 146169 Sodium nitroprusside ACS/AR

CAS 13755-38-9
$Na_2[Fe(CN)_5NO].2H_2O$ 99% F.W.297.95

Maximum Limits	
Insoluble Matter	0.01%
Chloride (Cl)	0.02%
Sulfate (SO_4)	Passes test (limit about 0.01%)

100	gm	6.90
500	gm	27.60

T 146363 Sodium periodate Lab-Grade

CAS 7790-28-5
$NaIO_4$ 98% F.W.213.89

100	gm	

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T146368 Sodium periodate ACS/AR

CAS 7790-28-5
$NaIO_4$ 99.8% F.W.213.89

Maximum Limits

Other halogens (as Cl)	0.02%
Manganese (Mn)	3 ppm

100	gm	12.30
6x100	gm	61.50

T146390 Sodium persulfate Lab-Grade

CAS 7775-27-1
UN-1505 IMDG - 5.1/III
$Na_2S_2O_8$ 98% F.W.238.09

Maximum Limits

Chloride (Cl)	0.005%
Lead (Pb)	0.005%
Iron (Fe)	0.01%

500	gm	5.75

T146395 Sodium persulfate ACS/AR

CAS 7775-27-1
UN-1505 IMDG - 5.1/III
$Na_2S_2O_8$ 99% F.W.238.09

500	gm	8.25

T146853 Sodium succinate Lab-Grade

CAS 6106-21-4
$(CH_2COONa)_2.6H_2O$ 99% F.W.270.14

500	gm	6.60

T146891 Sodium sulfate anhydrous Lab-Grade

CAS 7757-82-6
Na_2SO_4 99% F.W.142.04

500	gm	1.95

T146896 Sodium sulfate anhydrous ACS/AR

CAS 7757-82-6
Na_2SO_4 99.0% F.W.142.04
pH of a 5% solution at 25°C 5.2-9.2

Maximum Limits

Insoluble matter	0.001%
Loss on Ignition	0.5%
Chloride (Cl)	0.001%
Nitrogen compounds (as N)	5 ppm
Arsenic (As	1 ppm
Calcium , magnesium, and R_2O_3 precipitate	0.02%
Heavy metals (as Pb)	5 ppm
Iron (Fe)	0.001%

500	gm	3.15
6x500	gm	15.75

T146905 Sodium Sulfide flakes Lab-Grade

$Na_2S.XH_2O$
CAS 1313-84-4
UN -1385 IMDG - 4.2/II
Assay Min. 52%

500	gm	2.45

T146922 Sodium sulfite anhydrous ACS/AR

CAS 7757-83-7
Na_2SO_3 98% F.W.126.04

Maximum Limits

Insoluble matter	0.005%
Free acid	Passes test
Titrable free base	0.03 meq/g
Chloride (Cl)	0.02%
Arsenic (As)	1 ppm
Heavy metals (as Pb)	0.001%
Iron (Fe)	0.001%

500	gm	4.30
6x500	gm	21.50

T147062 Sodium thiosulphate pentahydrate Lab-Grade

CAS 10102-17-7
$Na_2S_2O_3.5H_2O$ 99-100.5% F.W.248.17

Maximum Limits

Calcium (Ca)	Passes test
Arsenic (As)	3 ppm
Heavy metals (as Pb)	0.002%
Lead	0.001%
Selenium	0.003%

500	gm	1.70

T147067 Sodium thiosulphate pentahydrate ACS/AR

CAS 10102-17-7
$Na_2S_2O_3.5H_2O$ 99.5% F.W.248.17

Maximum Limits

Insoluble matter	0.005%
Nitrogen compounds (as N)	0.002%
Sulfate and sulfite (as SO_4)	0.1%
Sulfide (S)	Passes test (limit about 1 ppm

500	gm	5.15

T147113 Sodium tripolyphosphate Lab-Grade

CAS 7758-29-4
$Na_5O_{10}P_3$

500	gm	4.20

T147265 Sodium tungstate hydrate Lab-Grade

CAS 10213-10-2
$Na_2WO_4.2H_2O$ 98% F.W.329.86

100	gm	3.45
500	gm	13.80

T147270 Sodium tungstate hydrate ACS/AR

CAS 10213-10-2
$Na_2WO_4.2H_2O$ 99.0 - 101% F.W.329.86

Maximum Limits

Insoluble matter	0.01%
Titrable free base	0.02%
Chloride (Cl)	0.005%
Molybdenum (Mo)	0.001%
Nitrogen compounds (as N)	0.001%
Sulfate (SO_4)	0.01%
Arsenic (As)	5 ppm
Heavy metals and iron (as Pb)	0.001%

100	gm	4.75

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 147732 Stannous chloride ACS/AR

CAS 10025-69-1
$SnCl_2.2H_2O$ 97% F.W.225.63

Maximum Limits

Solubility in hydrochloric acid	Passes test
Sulfate (SO_4)	Passes test (limit about 0.003%)
Arsenic (As	2 ppm
Substances not precipitated by hydrogen sulfide (as sulfates)	0.05%
Iron (Fe)	0.003%
Other metals (as Pb)	0.01%

100	gm	3.45
500	gm	13.80
6x500	gm	69.00

T 147855 Starch soluble Lab-Grade

CAS 9005-25-8
$(C_6H_{10}O_5)_n$

500	gm	8.00

T 147860 Starch soluble ACS/AR

CAS 9005-25-8
$(C_6H_{10}O_5)_n$

pH of a 2% solution @ 25°C	5.0-7.0
Sensitivity	Passes test
Solubility	Passes test

Maximum Limit

Residue after Ignition	0.4%

500	gm	10.75
6x500	gm	53.75

T 147890 Stearic acid for synthesis Lab-Grade

CAS 57-11-4
$CH_3(CH_2)_{16}COOH$ 98% F.W.284.48

500	gm	4.90

T 148298 Strontium carbonate Lab-Grade

CAS 1633-05-2
$SrCO_3$ 99% F.W.147.63

500	gm	8.30

T 148221 Strontium chloride Lab-Grade

CAS 10025-70-4
$SrCl_2.6H_2O$ 98-101% F.W.266.62

500	gm	4.60

T 148226 Strontium chloride ACS/ACR

CAS 10025-70-4
$SrCl_2.6H_2O$ 99.0-103.0% F.W.266.62

Maximum Limits

Insoluble matter	0.005%
Sulfate (SO_4)	0.001%
Barium (Ba)	0.05%
Calcium (Ca)	0.05%
Heavy metals (as Pb)	5 ppm
Iron (Fe)	5 ppm
Magnesium (Mg)	2 ppm

500	gm	11.00

T 148337 Strontium nitrate anhydrous Lab-Grade

CAS 10042-76-9
UN-1507 IMDG - 5.1/III
$Sr(NO_3)_2$ 99% F.W.211.63

500	gm	4.45

T 148492 Strontium sulfate Lab-Grade

CAS 7759-02-6
$SrSO_4$ F.W.183.68

500	gm	9.00

T 148330 Succinic acid ACS/AR

CAS 110-15-6
$HOOCCH_2CH_2COOH$ 99.0% F.W.118.09

Maximum Limits

Insoluble matter	0.01%
Residue after ignition	0.02%
Chloride (Cl)	0.001%
Phosphate (SO_4)	0.001%
Sulfate (SO_4)	0.003%
Nitrogen compounds (as N)	0.001%
Heavy metals (as Pb)	5 ppm
Iron (Fe)	5 ppm

100	gm	6.60
500	gm	26.10

T 148863 Sucrose Lab-Grade

CAS 57-50-1
$C_{12}H_{22}O_{11}$ 99.9% F.W.342.3

500	gm	2.00
6x500	gm	10.00

T 148868 Sucrose ACS/AR

CAS 57-50-1
$C_{12}H_{22}O_{11}$ 99% F.W.342.3

Specific rotation $[\alpha]_D$	66.3° to 66.8°

Maximum Limits

Insoluble matter	0.005%
Loss on Drying @105°C	0.03%
Residue after Ignition	0.01%
Titrable acid	0.0008 meq/g
Chloride (Cl)	0.005%
Sulfate and Sulfite (as SO_4)	0.005%
Heavy metal (as Pb)	5 ppm
Iron (Fe)	5 ppm
Invert sugar	0.05%

500	gm	6.90

T 149186 Sulfanilic acid ACS/AR

CAS 121-57-3
$NH_2.C_6H_4.SO_3H$ 98.0-102.0% F.W.173.19

Maximum Limits

Residue after ignition	0.01%
Insoluble in sodium carbonate solution	0.02%
Chloride (Cl)	0.002%
Nitrite (NO_4)	0.5 ppm
Sulfate (SO_4)	0.01%

100	gm	8.25
500	gm	33.00
6x500	gm	165.00

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T149625 Sulfur powder Lab-Grade

CAS 7704-34-9
S — F.W.32.06

100	gm	0.45
500	gm	1.60

T149656 Sulfuric acid 98% Lab-Grade

CAS 7664-93-9
UN-1830 IMDG - 8/II
H_2SO_4 — 98% — F.W.98.07

2x500	ml	4.40
8x500	ml	15.40
2.5	lt	6.10
4x2.5	lt	21.25
5	lt	8.50

T149661 Sulfuric acid 98% ACS /AR

S 7664-93-9
UN - 1830 IMDG - 8/II
H_2SO_4 — 95-0-98.0% — F.W.98.07

Maximum Limits

Color (APHA)	10
Residue after ignition	5 ppm
Chloride (Cl)	0.2 ppm
Nitrate (NO_3)	0.5 ppm
Ammonium (NH_4)	2 ppm
Substances reducing permanganate	2 ppm as SO_2
Arsenic (As)	0.01%
Heavy metals (as Pb)	1 ppm
Iron (Fe)	0.2 ppm
Mercury (Hg)	5 ppb

2x500	ml	5.00
8x500	ml	17.50
2.5	lt	7.20
4x2.5	lt	25.00
5	lt	10.10

T149670 Sulphosalicylic Acid 3% solution

125	ml	1.00
4x125	ml	3.00

T152591 Tetrahydrofuran ACS /AR

CAS 109-99-9
UN-2056 IMDG - 3.1/II
C_4H_8O — 99.0% — F.W.72.11

Maximum Limits

Color (APHA)	20
Peroxide (as H_2O_2)	0.015%
Residue after evaporation	0.03%
Water	0.05%

500 ml — 10.00

T155262 Thionyl chloride Lab-Grade

CAS 7719-09-7
UN - 1836 IMDG 8/I
$SOCl_2$ — 99-101% — F.W.118.97

500 ml — 6.00

T155415 Thiourea Lab-Grade

CAS 62-56-6
NH_2CSNH_2 — 99-101% — F.W.76.12

500 gm — 7.90

T155420 Thiourea ACS/AR

CAS 62-56-6
F.W. 76.12

NH_2CSNH_2	
Assay	min. 99.0%
Sulphate	0.01%
Iron	0.0005%

500	gm	13.15
6x500	gm	65.75

T155501 Thymol Crystals Lab-Grade

CAS 89-83-8
F.W.150.22

$C_{10}H_{14}O$	
Assay (GC)	min. 99.5%
M.P.	min. 49 deg C
Acidity (HCl)	0.073%

25	gm	4.70
100	gm	14.30

T155651 Thymol Blue solution Standard

pH transition range:
pH 1.2 - 2.8 — Violet red to brownish yellow
pH 7.8 - 9.5 — Greenish yellow to blue

125	ml	1.20
4x125	ml	3.60

T155621 Thymol Blue powder Lab-Grade

pH transition range:
CAS 76-61-9
F.W. 466.60

$C_{27}H_{30}O_5S$
pH transition range:
pH 1.2 - 2.8 — Violet red to brownish yellow
pH 7.8 - 9.5 — Greenish yellow to blue

1	gm	0.70
5	gm	2.90

T155430 Thymolphthaleine indicator solution

125	ml	1.30
4x125	ml	3.90

T155450 Titan yellow solution

pH 12.0-13.0 yellow to red

125	ml	1.50
4x125	ml	3.50

T155980 o-Tolidine ACS/AR

CAS 119-93-7
$[NH_2C_6H_3(CH_3)]_2$ — 97.5% — F.W.212.30
Melting range — 129°-131°C
Sensitivity to Chlorine — Passes test
Maximum Limit
Residue after Ignition — 0.1%

25	gm	1.80
100	gm	5.45

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T 156106 Toluene ACS/AR

CAS 108-88-3
UN-1294 IMDG - 3.2/II
$C_6H_5CH_3$ 99.5% F.W.92.14

Maximum Limits

Color (APHA)	10
Residue after evaporation	0.001%
Substance darkened by sulfuric acid	Passes test
Sulfur compounds (as S)	0.003%
Water (H_2	0.03%

500	ml	2.55
6x500	ml	12.75
2.5	lt	11.30

T 157981 Trichloroethylene for synthesis Lab-Grade

CAS 79-01-6
UN-1710 IMDG0 6.1/III
$CHCl=CCl_2$ 99% F.W.131.39

500	ml	3.60
6x500	ml	18.00
2.5	lt	15.45

T 158700 Triethanolamine Lab-Grade

CAS 102-71-6
$N(CH_2CH_2OH)_3$ 95% F.W.149.19

500	ml	4.60

T 158720 Triethylamine for synthesis Lab-Grade

CAS 121-44-8
UN-1296 IMDG - 3.2/II
$(C_2H_5)_3N$ 99% F.W.101.19

500	ml	4.15
2.5	lt	18.30

T 158725 Triethylamine for synthesis ACS/AR

CAS 121-44-8
UN-1296 IMDG - 3.2/II
$(C_2H_5)_3N$ 99.5% F.W.101.19

Maximum Limits

Water (H_2O)	0.05%
Iron (Fe)	0.0001%
Lead (Pb)	0.0001%

500	ml	6.60
6x500	ml	33.00

T 163250 Universal indicator solution pH 2.0-10.0 Lab-Grade

500	ml	1.00

T 163263 Urea ACS /AR

CAS 57-13-6
$(NH_2)_2CO$ 99.5% F.W.60.06
Melting point Not below 132°C nor above 135°C

Maximum Limits

Insoluble matter	0.01%
Residue after ignition	0.01%
Chloride (Cl)	5 ppm
Sulfate (SO_4)	0.001%
Heavy metals (as Pb)	0.001%
Iron (Fe)	0.001%

500	gm	5.45
6x500	gm	27.25

T 164501 Wright Stain Lab-Grade

CAS 68988-92-1
Absorptivity (1%/1 cm: methanol dried) :
(g) max. 640-651 nm :1200-1400
(g) max. 521-524 nm : 650-850

5	gm	1.55
25	gm	6.30

T 164505 Wright's Staining solution

125	ml	1.00
4x125	ml	3.00

T 167228 Xylenes ACS /AR

CAS 1330-20-7
UN-1307 IMDG-3.2/II
$C_6H_4(CH_3)_2$ 98.5% F.W.106.17

Maximum Limits

Color (APHA)	10%
Residue after evaporation	0.002%
Substances darkened by sulfuric acid	Passes test
Sulfur compunds (as S)	0.003%
Water (H_2O)	0.05%

500	ml	2.75
6x500	ml	13.75
2.5	lt	12.45

T 167214 Xylenes rectified Lab-Grade

CAS 1330-20-7
UN-1307 IMDG - 3.2/II
$C_6H_4(CH_3)_2$ 98.5% F.W.106.17

500	ml	2.35
2.5	lt	11.40

T 167221 Xylenes Sulfur free Lab-Grade

CAS 1330-20-7
UN-1307 IMDG - 3.2/II
$C_6H_4(CH_3)_2$ 98.5% F.W.106.17

500	ml	2.40
2.5	lt	11.50

T 167250 Xylenol Orange indicator solution 0.1%

125	ml	2.50
4x125	ml	7.50

T 169011 Zinc (metal) dust Lab-Grade

CAS 7440-66-6
UN-1436 IMDG -4.3/II
Zn 90% F.W.65.39

500	gm	5.30

T 169016 Zinc (metal) dust ACS/AR

CAS 7440-66-6
UN-1436 IMDG - 4.3/II
Zn 95% F.W.65.39

500	gm	5.75

(INTERNATIONAL PRICE LIST IN US. DOLLARS)

T. BAKER LAB CHEMICALS

T169005 Zinc (metal) granulated (As Free) Lab-grade

CAS 7440-66-6

Zn	99%	F.W.65.37

500	gm	5.90

T169010 Zinc (metal) granulated (As Free) ACS/AR

CAS 7440-66-6

Zn	99.8%	F.W.65.37
Suitability for Determination of Arsenic (As)		Passes test
Maximum Limits		
Iron (Fe)		0.01%
Lead (Pb)		0.01%

500	gm	6.90

T169024 Zinc acetate Lab-Grade

CAS 5970-45-6

$(CH_3COO)_2Zn.2H_2O$	98.5%	F.W.219.50

500	gm	3.60

T169029 Zinc acetate ACS

CAS 5970-45-6

$(CH_3COO)_2Zn.2H_2O$	98.0%	F.W.219.50
pH of a 5% solution at 25°C		6.0 -7.0
Maximum Limits		
Insoluble matter		0.005%
Chloride (Cl)		5 ppm
Sulfate (SO_4)		0.005%
Arsenic (As)		0.5 ppm
Calcium (Ca)		0.005%
Iron (Fe)		5 ppm
Lead (Pb)		0.002%
Magnesium (Mg)		0.005%
Potassium K)		0.01%
Sodium (Na)		0.01%

500	gm	5.75
6x500	gm	28.75

T169143 Zinc carbonate basic Lab-Grade

CAS 12539-71-8

$ZnCO_3.2ZnO.3H_2O$	65%
Maximum Limit	
Sulfate (SO_4)	0.5%

500	gm	5.00

T169158 Zinc Chloride dry Lab-Grade

CAS 7646-85-7

$ZnCl_2$

UN-2331 IMDG - 8/III

	F.W. 136.29
Assay	Min. 94-96%

500	gm	2.70

T169577 Zinc oxide Lab-Grade

CAS 1314-13-2

ZnO	99.0%	F.W.81.39

500	gm	3.75

T169582 Zinc oxide ACS/AR

CAS 1314-13-2

ZnO	99.0%	F.W.81.39
Maximum Limits		
Insoluble in dilute sulfuric acid		0.01%
Alkalinity		Passes test
Chloride (Cl0		0.001%
Nitrate (NO_3)		0.003%
Sulfur compounds (as SO_4)		0.01%
Arsenic (As)		2 ppm
Calcium (Ca)		0.005%
Iron (Fe)		0.001%
Lead (Pb)		0.005%
Magnesium (Mg)		0.005%
Manganese (Mn)		5 ppm
Potassium (K)		0.01%
Sodium (K)		0.05%

500	gm	4.60
6x500	gm	23.00

T169722 Zinc sulfate heptahydrate Lab-Grade

CAS 7446-20-0

$ZnSO_4.7H_2O$	99%	F.W.287.56

500	gm	2.15

T169727 Zinc sulfate heptahydrate ACS/AR

CAS 7446-20-0

$ZnSO_4.7H_2O$	99.0-103.0%	F.W.287.56
Maximum Limits		
Insoluble matter		0.01%
Chloride (Cl)		5 ppm
Nitrate (NO_3)		0.002%
Ammonium (NH_4)		0.001%
Arsenic (As)		1 ppm
Calcium (Ca)		0.005%
Iron (Fe)		0.001%
Lead (PB)		0.003%
Magnesium (Mg)		0.005%
Manganese (Mn)		3 ppm
Potassium (K)		0.01%
Sodium (Na)		0.05%

500	gm	4.15
6x500	gm	20.75

M 100	Chip Chap Educational Electronic Kit	20.00 Each
M 101	Light Lab Kit (Optics 40 experiments)	55.00 Each
M 102	Electric Kit (60 experiments)	24.00 Each
M 103	Maglite Kit (20 experiements)	8.00 Each
M 104	Bell Kit	6.00 Each
M 105	Electric Wiring Kit	6.00 Each
M 106	Tele Kit	9.00 Each

T BAKER LAB CHEMICALS

Manufacturer of Laboratory & Fine Chemicals

Periodic Table of the Elements

Non-metal | Metal

Key

Common Oxidation States → +3 13 ← Atomic Number
Atomic Weight → Al 26.981539 ← Atomic Symbol
Electron Configuration of Outer Shells → 2-8-3

1/Ia	2/IIa	3/IIIb	4/IVb	5/Vb	6/VIb	7/VIIb	8/VIII	9/VIII	10/VIII	11/Ib	12/IIb	13/IIIa	14/IVa	15/Va	16/VIa	17/VIIa	18/VIIIa/0
+1 H 1 1.00794 1 Hydrogen																	0 He 2 4.002602 2 Helium
+1 Li 3 6.941 2-1 Lithium	+2 Be 4 9.012182 2-2 Beryllium											+3 B 5 10.811 2-3 Boron	+2 +4 C 6 12.011 2-4 Carbon	+1 +2 +3 +4 +5 N 7 14.00674 2-5 Nitrogen	-2 O 8 15.9994 2-6 Oxygen	-1 F 9 18.9984032 2-7 Fluorine	0 Ne 10 20.1797 2-8 Neon
+1 Na 11 22.989768 2-8-1 Sodium	+2 Mg 12 24.3050 2-8-2 Magnesium											+3 Al 13 26.981539 2-8-3 Aluminium	+2 +4 Si 14 28.0855 2-8-4 Silicon	+3 +5 P 15 30.973762 2-8-5 Phosphorus	+4 +6 -2 S 16 32.066 2-8-6 Sulphur	+1 +3 +5 +7 Cl 17 35.4527 2-8-7 Chlorine	0 Ar 18 39.948 2-8-8 Argon
+1 K 19 39.0983 -8-8-1 Potassium	+2 Ca 20 40.078 -8-8-2 Calcium	+3 Sc 21 44.955910 -8-9-2 Scandium	+2 +3 +4 Ti 22 47.867 -8-10-2 Titanium	+2 +3 +4 +5 V 23 50.9415 -8-11-2 Vanadium	+2 +3 +6 Cr 24 51.9961 -8-13-1 Chromium	+2 +3 +4 +6 +7 Mn 25 54.93805 -8-13-2 Manganese	+2 +3 Fe 26 55.845 -8-14-2 Iron	+2 +3 Co 27 58.93320 -8-15-2 Cobalt	+2 +3 Ni 28 58.6934 -8-16-2 Nickel	+1 +2 Cu 29 63.546 -8-18-1 Copper	+2 Zn 30 65.39 -8-18-2 Zinc	+3 Ga 31 69.723 -8-18-3 Gallium	+2 +4 Ge 32 72.61 -8-18-4 Germanium	+3 +5 As 33 74.92159 -8-18-5 Arsenic	+4 +6 -2 Se 34 78.96 -8-18-6 Selenium	+1 +5 +7 Br 35 79.904 -8-18-7 Bromine	0 Kr 36 83.80 -8-18-8 Krypton
+1 Rb 37 85.4678 -18-8-1 Rubidium	+2 Sr 38 87.62 -18-8-2 Strontium	+3 Y 39 88.90585 -18-9-2 Yttrium	+4 Zr 40 91.224 -18-10-2 Zirconium	+3 +5 Nb 41 92.90638 -18-12-1 Niobium	+6 Mo 42 95.94 -18-13-1 Molybdenum	+4 +6 +7 Tc 43 (97.90721) -18-13-2 Technetium	+3 Ru 44 101.07 -18-15-1 Ruthenium	+3 Rh 45 102.90550 -18-16-1 Rhodium	+2 +4 Pd 46 106.42 -18-18-0 Palladium	+1 Ag 47 107.8682 -18-18-1 Silver	+2 Cd 48 112.411 -18-18-2 Cadmium	+3 In 49 114.818 -18-18-3 Indium	+2 +4 Sn 50 118.710 -18-18-4 Tin	+3 +5 Sb 51 121.760 -18-18-5 Antimony	+4 +6 -2 Te 52 127.60 -18-18-6 Tellurium	+1 +5 +7 I 53 126.90447 -18-18-7 Iodine	0 Xe 54 131.29 -18-18-8 Xenon
+1 Cs 55 132.90543 -18-8-1 Cesium	+2 Ba 56 137.327 -18-8-2 Barium	57-71 See Lantha-nides	+4 Hf 72 178.49 -32-10-2 Hafnium	+5 Ta 73 180.9479 -32-11-2 Tantalum	+6 W 74 183.84 -32-12-2 Tungsten	+4 +6 +7 Re 75 186.207 -32-13-2 Rhenium	+3 Os 76 190.2 -32-14-2 Osmium	+3 +4 Ir 77 192.217 -32-15-2 Iridium	+2 +4 Pt 78 195.08 -32-16-2 Platinum	+1 +3 Au 79 196.96654 -32-18-1 Gold	+1 -2 Hg 80 200.59 -32-18-2 Mercury	+1 +3 Tl 81 204.3833 -32-18-3 Thallium	+2 +4 Pb 82 207.2 -32-18-4 Lead	-3 +5 Bi 83 208.98037 -32-18-5 Bismuth	+2 +4 Po 84 (208.9824) -32-18-6 Polonium	+1 +3 +5 +7 At 85 (209.9871) -32-18-7 Astatine	0 Rn 86 (222.0176) -32-18-8 Radon
+1 Fr 87 (223.0197) -18-8-1 Francium	+2 Ra 88 (226.0254) -18-8-2 Radium	89-103 See Actinides	+4 *Rf 104 -32-10-2 Rutherfordium	*Ha 105 (262.114) -32-11-2 Hahnium	*Unh 106 (263.118) -32-12-2 Unnilhexium	*Ns 107 (262.12) -32-13-2 Nielsbohrium	*Hs 108 (265.00) -32-14-2 Hassium	*Mt 109 266.00 -32-15-2 Meitnerium	*Uun 110 272.00 -32-16-2 Ununnilium								

Noble Gases

Elements 104-110 : Relatively recent elements.
Based on 1987 IUPAC Table of Standard Atomic Weights of the Elements Updated for the Information available till 1994.
*Relative atomic mass of the isotope of that element of longest known half-life.

Metal — Isolopes

Lanthanides	+3 57 Lu 138.9055 -18-9-2 Lanthanum	+3 +4 58 Ce 140.115 -20-8-2 Cerium	+3 59 Pr 140.90765 -21-8-2 Praseodymium	+3 60 Nd 144.24 -22-8-2 Neodymium	+3 61 Pm (144.9127) -23-8-2 Promethium	+2 +3 62 Sm 150.36 -24-8-2 Samarium	+2 +3 63 Eu 151.965 -25-8-2 Europium	+3 64 Gd 157.25 -25-9-2 Gadolinium	+3 65 Tb 158.92534 -27-8-2 Terbium	+3 66 Dy 162.50 -28-8-2 Dysprosium	+3 67 Ho 164.93032 -29-8-2 Holmium	+3 68 Er 167.26 -30-8-2 Erbium	+3 69 Tm 168.93421 -31-8-2 Thulium	+2 +3 70 Yb 173.04 -32-8-2 Ytterbium	+3 71 Lu 174.967 -32-9-2 Lutetium
Actinides	+3 89 Ac (227.0278) -18-9-2 Actinium	+4 90 Th 232.0381 -18-10-2 Thorium	+4 +5 91 Pa (231.0388) -20-9-2 Protactinium	+3 +4 +5 +6 92 U 238.0289 -21-9-2 Uranium	+3 +4 +5 +6 93 Np (237.0482 -22-9-2 Neptunium	+3 +4 +5 +6 94 Pu (244.0642 -24-8-2 Plutonium	+3 +4 +5 +6 95 Am (243.0614) -25-8-2 Americium	+3 96 Cm (247.0703) -25-9-2 Curium	+3 +4 97 Bk (247.0703) -27-8-2 Berkelium	+3 98 Cf (251.0796) -28-8-2 Californium	+3 99 Es (252.083) -29-8-2 Einsteinium	+3 100 Fm (257.0951) -30-8-2 Fermium	+2 +3 101 Md (258.10) -31-8-2 Mendelevium	+2 +3 102 No (259.1009) -32-8-2 Nobelium	+3 103 Lr (262.11) -32-9-2 Lawrencium

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DIS-13-13

Dr. Reddy's
LABORATORIES

DocteRe

Docetaxel 20 mg & 80 mg

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DocetaRe

Docetaxel 20 mg & 80 mg

ABRIDGED PRODUCT INFORMATION:

Description Docetaxel (DOCETERE) is a new semi synthetic analogue of Paclitaxel with promising antitumour activity.

Composition

Each single dose vial contains:	Docetere 80	Docetere 20
Docetaxel Trihydrate equivalent to Docetaxel anhydrous	80 mg.	20 mg.
Polysorbate 80	2.0 mL.	0.5 mL.

Mode of Action DOCETERE enhances polymerization of the tubulin into stable microtubules and inhibits their depolymerization. This induces the formation of stable microtubule bundles leading to cell death.

Indications DOCETERE in indicated in the treatment of patients with metastatic breast cancer and non-small cell lung cancer.

Adverse Reactions Neutropenia, fluid retention, peripheral neuropathy, hypersensitivity reactions, nail changes, asthenia, mucositis and alopecia.

Storage Unopened vials should be stored under refrigeration at a temperature of 2°- 8°C. Solvent for Docetaxel injection concentrate should be stored in a cool place, protected from light.

Presentations DOCETERE 80 mg. carton containing single dose Docetaxel-80 mg. vial and a carton containing solvent for Docetaxel injection concentrate - 6 mL.

DOCETERE 20 mg. carton containing single dose Docetaxel-20 mg. vials and carton containing solvent for Docetaxel injection concentrate - 1.5 mL.

PREPARATION FOR THE INTRAVENOUS ADMINISTRATION

(A) PREPARATION OF THE DOCETETRE PREMIX SOLUTION (10 mg. DOCETAXEL / mL

A-1 Remove the required number of DOCETERE vials from the refrigerator and allow to stand at room temperature for 5 minutes.

A-2 Use a syringe fitted with needle, aseptically withdraw the entire contents of the solvent from "SOLVENT FOR DOCETAXEL" vial.

A-3 Inject the entire contents of the syringe into the corresponding DOCETERE vial

A-4 Remove the syringe and needle and shake the mixture manually for 15 seconds.

A-5 Allow the premix vial to stand for 5 minutes at room temperature and then check that the solution is homogenous and clear. (Foaming is normal even after 5 minutes due to the presence of polysorbate 80 in the formulation. The premix solution contains 10 mg. / mL docetaxel and is stable for 8 hours in a refrigerator or at room temperature.

(B) PREPARATION OF THE INFUSION SOLUTION

B-1 More than one premix vial may be necessary to obtain the required dose for the patient. Based on the required dose for the patient expressed in mg., aseptically withdraw the corresponding premix volume containing 10 mg./mL. docetaxel from the appropriate number of premix vials using graduated syringes fitted with a needle. For example, a dose of 140 mg. docetaxel would require 14 mL docetaxel premix solution.

B-2 Inject the required premix volume into a 250 mL infusion bag or bottle containing either 5% glucose solution or 0.9% sodium chloride solution. If a dose greater than 240 mg. of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.9 mg./mL. docetaxel is not exceeded.

B-3 Mix the infusion bag or bottle manually using a rocking motion.

B-4 The DOCETERE infusion solution should be aseptically administered intravenously as soon as possible after preparation as a 1 hour infusion under room temperature and normal lighting conditions.

B-5 As with all parenteral products, DOCETERE premix solution and infusion solution should be visually inspected prior to use, solutions containing a precipitate should be discarded.

DISPOSAL

All materials that have been utilised for dilution and administration should be disposed of according to standard procedures.

For further information, please write to: Docetere Cell, **Dr. REDDY'S LABORATORIES LTD.,**
8-2-337, Road No. 3, Banjara Hills, Hyderabad-500 034. Phone: 040-3358471 Fax: 040-3358472 email: drlpmt@hotmail.com

A Phase II Study of Docetaxel in Patients With Paclitaxel-Resistant Metastatic Breast Cancer

By Vicente Valero, Stephen E. Jones, Daniel D. Von Hoff, Daniel J. Booser, Robert G. Mennel, Peter M. Ravdin, Frankie A. Holmes, Zia Rahman, Margaret W. Schottstaedt, John K. Erban, Laura Esparza-Guerra, Robert H. Earhart, Gabriel N. Hortobagyi, and Howard A. Burris III

Purpose: To evaluate the efficacy and safety of docetaxel in patients with paclitaxel-resistant metastatic breast cancer (MBC).

Patients and Methods: Docetaxel (100 mg/m²) was administered every 3 weeks to 46 patients registered at four centers. Patients had previously received ≤ two chemotherapy regimens for MBC. All patients had progressive disease while receiving paclitaxel therapy. Treatment was repeated until there was evidence of disease progression or for a maximum of three cycles after best response.

Results: Objective responses were seen in eight of 44 assessable patients (18.1%; 95% confidence interval [CI], 6.7% to 29.5%). Seven patients had partial responses and one patient responded completely. Response rates were not significantly different by previously received paclitaxel dose or resistance. No responses were seen in 12 patients who had previously received paclitaxel by 24-hour infusion, but the response rate in 32 patients who had received paclitaxel by 1- to 3-hour infusion was 25%. The median response duration was 29 weeks and the median time to disease progression was 10 weeks. Median survival was 10.5 months. Clinically significant (severe) adverse events included neutropenic fever (24% of patients), asthenia (22%), infection (13%), stomatitis (9%), neurosensory changes (7%), myalgia (7%), and diarrhea (7%).

Conclusion: Docetaxel is active in patients with paclitaxel-resistant breast cancer, particularly in those who failed to respond to brief infusions of paclitaxel. Response rates were comparable to or better than those seen with other therapies for patients with paclitaxel-resistant MBC. This confirms preclinical studies, which indicated only partial cross-resistance between paclitaxel and docetaxel.

J Clin Oncol 16:3362-3368.

DOCETAXEL AND PACLITAXEL are cytotoxic agents that interfere with microtubular function by promoting tubulin polymerization and inhibiting the depolymerization of microtubules. Although their mechanism of action is similar, the preclinical and clinical activity profiles of the two compounds have several notable differences.[1-5] Docetaxel is a more potent promoter of tubulin polymerization and a more potent inhibitor of microtubule depolymerization than paclitaxel.[6,7] In addition, docetaxel has a greater affinity than paclitaxel for the tubulin-binding site and it promotes structurally different microtubules than does paclitaxel.[5-6,8] The intracellular biologic activity of the taxanes is related to their concentration and duration of exposure, especially in taxane-resistant cell lines. The cellular uptake of docetaxel is greater than that of paclitaxel and its efflux rate is about three times slower than that of paclitaxel.[9] These differences may result in higher intracellular concentration and longer exposure to docetaxel, which may, among other biologic differences, lead to greater cytotoxic activity. In many in vitro murine and human preclinical models, including chemotherapy-resistant cell lines, docetaxel demonstrated greater antitumor activity than paclitaxel at equitoxic doses.[4,10-12] Docetaxel was capable of inducing *bcl-2* phosphorylation and apoptotic cell death at 100-fold lower concentrations than paclitaxel.[13] Docetaxel was also shown to be more potent than paclitaxel in many tumor models in vivo.[3,14-16] Docetaxel was less schedule-dependent than paclitaxel and showed a stronger correlation between dose and plasma concentration and area under the plasma concentration-time curve (AUC).[1-2,5,17] Finally, preclinical studies indicated only partial cross-resistance between paclitaxel and docetaxel in cell lines in which resistance to paclitaxel had been induced.[1,14]

Clinical differences between docetaxel and paclitaxel are more difficult to define because no randomized phase III study comparing these agents has been completed. Both drugs were active in first- and second-line treatment of patients with metastatic breast, ovarian, and lung cancers. Phase II studies showed greater efficacy for docetaxel

From The University of Texas M.D. Anderson Cancer Center, Houston; Texas Oncology Physician Association, Dallas; Cancer Therapy and Research Center, San Antonio, TX; New England Medical Center, Boston, MA; and Rhône-Poulenc Rorer Pharmaceuticals, Inc, Collegeville, PA.

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0732-183X/98/1610-0034$3.00/0

relative to paclitaxel in patients with anthracycline-resistant breast cancer.[1] In patients with anthracycline-resistant metastatic breast cancer (MBC) treated with docetaxel at a dose of 100 mg/m^2 infused over 1 hour every 3 weeks, objective response rates ranged from 32% to 51%.[18-20]

The use of paclitaxel in anthracycline-resistant patients has also been studied. When the same definition of anthracycline resistance was used, paclitaxel doses of 175 to 300 mg/m^2 administered over 3 to 24 hours resulted in response rates that ranged from 6% to 30%.[21,22] These preclinical and clinical results led to implementation of the present prospective phase II study at four centers in the United States. The objectives of the study were to evaluate the objective response rate, duration of response, and toxicity of docetaxel in patients with paclitaxel-resistant metastatic breast cancer. The final study results are reported here.

PATIENTS AND METHODS

Eligibility Criteria

Eligibility criteria included histologically confirmed, advanced breast cancer resistant to paclitaxel therapy in female patients ≥ 18 years of age. Patients were required to have at least one bidimensionally measurable indicator lesion that had not been irradiated, a Karnofsky performance status ≥ 60%, no peripheral neuropathy ≥ National Cancer Institute (NCI) grade 2, no symptomatic pleural effusion, and to have undergone no more than two previous chemotherapy regimens for advanced disease (in addition to any adjuvant and/or neoadjuvant therapy), with a paclitaxel-based regimen having been the most recent treatment. Patients had to have adequate bone marrow function (absolute neutrophil count ≥ 1,500 cells/μL, platelet count ≥ 100,000 cells/μL), hepatic function (normal total bilirubin, AST ≤ 1.5 times upper limit of normal, and alkaline phosphatase ≤ five times upper limit of normal), and kidney function (creatinine concentration ≤ 2.0 mg/dL). Patients must have had no radiation therapy within 3 weeks before study entry.

An interval of at least 21 days was required between the end of previous paclitaxel therapy and protocol entry. Paclitaxel resistance was defined as the patient's having experienced progressive disease while receiving paclitaxel with at least two cycles at doses of 135 to 250 mg/m^2. Primary resistance to paclitaxel was defined as no tumor response (disease progression). Secondary resistance was defined as stable disease, partial response, or complete response to paclitaxel preceding disease progression. Patients who had progressive disease after they discontinued paclitaxel therapy were not eligible for this protocol. Prestudy information to confirm disease progression on paclitaxel was reviewed by the principal investigators at each site. Before treatment began, all patients were advised of the investigational nature of the study and signed an institutional review board–approved informed consent.

Treatment Plan

Patients were pretreated with 8 mg of dexamethasone orally twice daily for 3 days beginning on the day before each docetaxel infusion. The starting dose of docetaxel was 100 mg/m^2 over 1 hour into a peripheral or central vein. Arterial blood pressure, pulse rate, and respiratory rate were measured before administration of docetaxel, every 15 minutes during administration, and 2 hours afterward. Dose reductions were made in subsequent cycles according to the system that showed the greatest degree of toxicity. A maximum of two 25% dose reductions for toxic effects (level 1, 75 mg/m^2; level 2, 55 mg/m^2) were allowed per patient. Docetaxel administration was repeated every 21 days until there was evidence of progressive disease or unacceptable toxicity, or for a maximum of three cycles after best response. Patients who enjoyed an objective response or stable disease were to receive at least six cycles of docetaxel. Patients with stable disease were to be removed from the study after six cycles or given additional cycles at the discretion of the investigator. Patients with rapidly progressive disease (ie, new lesions or a > 25% increase in sum of products of perpendicular diameters of measurable indicator lesions) were removed from the study after one cycle of therapy and were categorized as having progressive disease.

Study Evaluations

Pretreatment evaluations consisted of a complete medical history and physical examination, which included neurologic evaluation, complete blood cell count, biochemical profile, urinalysis, ECG, chest x-ray, bone scan, and computed tomographic scans of chest, abdomen, and brain (if indicated). At the end of every cycle, patients underwent a chest x-ray and biochemical profile, physical examination, tumor measurements, and toxicity evaluations. Patients had a complete blood cell count weekly during the first two cycles and then once before every cycle thereafter. Neurologic examinations were performed every two cycles. Imaging studies were done to assess objective response every two treatment cycles. An ECG was performed every four cycles.

Toxic effects were graded according to the NCI common toxicity criteria.[23] Other toxic effects were graded as mild (asymptomatic or minor symptoms; no treatment required), moderate (moderately symptomatic; minor treatment required), or severe (symptomatic and interfering with function; major treatment required).

Response Criteria

Responses were graded by standard criteria (complete response, partial response, stable disease or no change, and progressive disease).[24] The duration of complete response was calculated from the time of the first documentation of complete remission to the first documentation of progressive disease. The duration of partial response was calculated from the first docetaxel infusion to the first occurrence of progression. The time to progression was calculated from the time of the first docetaxel infusion to the first objective evidence of tumor progression. Responses were confirmed by an independent team of two oncologists and a radiologist.

Statistical Analysis

Continuous data were summarized using descriptive statistics. Confidence intervals (CIs) were constructed at the 95% level and Kaplan-Meier estimations were performed to analyze censored data. Subgroup analyses were performed on patients who had previous therapy with low-dose paclitaxel (≤ 175 mg/m^2) and those who had been treated with high-dose paclitaxel (> 175 mg/m^2). Patients were grouped according to duration of previous paclitaxel infusion (1 to 3 hours v 24 hours) for response analysis. For some analyses, patients were also grouped on the basis of primary or secondary paclitaxel resistance. All treated patients were analyzed for safety.

Table 1. Patient Characteristics

Characteristics	Overall		Previous Paclitaxel Dose ≤ 175 mg/m²		Previous Paclitaxel Dose > 175 mg/m²	
	No.	%	No.	%	No.	%
No. of patients	46		30		16	
Age, years						
Range	26-78		26-78		29-61	
Median	47.5		48.5		43.0	
Karnofsky status						
Unknown	1	2.2	1	3.3	0	0
60-80	16	34.8	10	33.3	6	37.5
90-100	29	63.0	19	63.4	10	62.5
No. of organs involved						
1	7	15.2	6	20.0	1	6.3
2	20	43.5	12	40.0	8	50.0
≥ 3	19	41.3	12	40.0	7	43.8
Site of disease						
Visceral	35	76.1	24	80.0	11	68.8
Liver	25	54.3	17	56.7	8	50.0
Lung	15	32.6	11	36.7	4	25.0
Pleura	2	4.3	1	3.3	1	6.3
Bone	17	37.0	10	33.3	7	43.8
Lymph nodes	21	45.7	13	43.3	8	50.1
Skin	10	21.7	6	20.0	4	25.0
Breast	11	23.9	5	16.7	6	37.5
Soft tissue	10	21.7	6	20.0	4	25.0
Previous chemotherapy						
Neoadjuvant/ adjuvant only	1	2.2	1	3.3	0	0
Advanced disease only	13	28.3	10	33.3	3	18.8
Neoadjuvant and/or adjuvant and advanced	32	69.6	19	63.3	13	81.3
No. of previous regimens						
1	2	4.3	2	6.7	0	0
2	26	56.5	13	43.3	13	81.3
3	18	39.1	15	50.0	3	18.8
Previous anthracycline exposure	41	89.1	27	90.0	14	87.5
Previous paclitaxel resistance						
Primary	18	39.1	14	46.7	4	25.0
Secondary	28	60.9	16	53.3	12	75.0

RESULTS

Patient Characteristics

Between April 1994 and December 1995, 46 patients were enrolled onto the study at four centers. Patient characteristics are listed in Table 1. The majority of patients (76.1%) had visceral-dominant disease with multiple disease sites. Most patients (95.6%) had received two or more chemotherapy regimens. Sixteen patients in the low-dose group (≤ 175 mg/m²) had received a median cumulative paclitaxel exposure of 700 mg/m² (range, 318 to 3,833 mg/m²) and 30 patients in the high-dose group (> 175 mg/m²) had been exposed to a median cumulative dose of 1,212.5 mg/m² (range, 400 to 4,355 mg/m²). Overall, the median cumulative paclitaxel exposure of the 46 patients in the study was 810 mg/m² (range, 318 to 4,355 mg/m²). Twelve patients had received paclitaxel by 24-hour infusion regimens and 34 had received 3-hour infusion regimens; none had received 96-hour infusions. The median time between the last dose of paclitaxel and the first dose of docetaxel was 1 month (range, 0.6 to 7.2); for 16 patients more than 1 month elapsed between the two taxane treatments.

Response

The overall response rate of the intent-to-treat population of 46 patients was 17.4% (95% CI, 7.8% to 31.4%). Forty-four patients were assessable for efficacy. Two patients were ineligible, one because of other malignancy and one because disease progression on paclitaxel could not be proved. One of these patients' response to docetaxel treatment was stable disease and one was partial response. Among the 44 patients who were assessable, two patients could not be assessed for response. Both were considered nonresponders. One of the other two patients had no follow-up data and another patient received only one treatment cycle.

The following analysis is based only on the patients who were assessable for efficacy. Among 44 assessable patients, the overall objective response rate was 18.1% (95% CI, 6.7% to 29.5%) (Table 2). One complete response and seven

Table 2. Objective Response Rate in Assessable Patients By Previous Paclitaxel Dose and Resistance

Response	Overall (N = 44)		Previous Paclitaxel Dose ≤ 175 mg/m² (n = 28)		Previous Paclitaxel Dose > 175 mg/m² (n = 16)		Primary Resistance (n = 17)		Secondary Resistance (n = 27)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Overall response rate	8	18.1	3	10.7	5	31.2	3	17.6	5	18.5
Complete response	1	2.2	1	3.5	0	0	1	5.9	0	0
Partial response	7	15.9	2	7.2	5	31.2	2	11.7	5	18.5
Stable	14	31.9	12	42.8	2	12.5	6	35.2	8	29.2
Progression	22	50	13	46.5	9	55.3	8	47.2	14	52.3

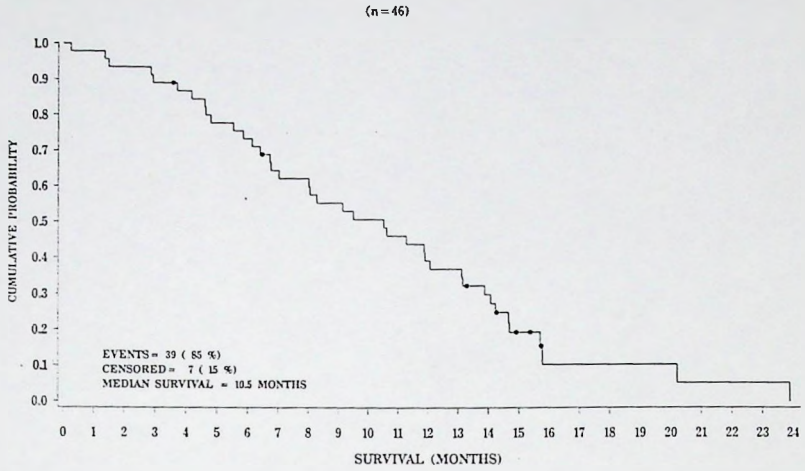

Fig 1. Survival analysis (intent to treat).

partial responses were observed. The time to response of individual patients ranged from 3 to 20 weeks (median, 6.5). The patient who experienced a complete response required 3 weeks to achieve a partial response and 9 weeks to attain a complete response.

The median duration of response was 29 weeks (range, 22 to 53). The median time to disease progression was 10 weeks (range, 3 to 53). Patients' previous paclitaxel dose level did not affect these results. The median survival time (intent to treat) was 10.5 months (range, 1.2 to 30+). A survival curve for all patients is presented in Fig 1.

Objective response rates by previous paclitaxel dose and resistance are listed in Table 2. When classified by duration of previous paclitaxel infusion, the response rate was 0% in the 24-hour infusion group (n = 12) and 25% in the 1- to 3-hour infusion group (n = 32). This difference was not statistically significant.

Safety Profile

A total of 199 cycles was assessable for toxic effects in 46 patients; docetaxel was administered at a dose of 100 mg/m^2 for 129 cycles, 75 mg/m^2 for 65 cycles, and 55 mg/m^2 for five cycles. The docetaxel dose was reduced from 100 mg/m^2 to 75 mg/m^2 in 19 patients (because of febrile neutropenia in nine, infection in three, stomatitis in one, diarrhea and rash in one, and neuropathy in five), and from 75 mg/m^2 to 55 mg/m^2 in four patients (because of infection in two and neuropathy in two).

Overall, 64.7% of the patients received at least three cycles of docetaxel. Nine delays occurred that were longer than 7 days (one because of a patient's upper respiratory infection, two because of stomatitis, one because of febrile neutropenia, one as a result of transient neuromotor symptoms, and four for unspecified reasons). The median cumulative dose of docetaxel was 388 mg/m^2 (range, 88 to 949 mg/m^2) and the median relative dose-intensity was 92% of the planned dose.

Three patients were withdrawn from the study because of neurosensory toxicity: one patient after four cycles, because of grade 3 neurotoxicity; one patient after eight cycles, because of grade 2 neurotoxicity; and one patient after two cycles, because she developed grade 2 neurotoxic symptoms. The latter two withdrawals were minor protocol violations. There were no drug-related deaths. One patient died 7 days after she received her initial docetaxel treatment because of her breast cancer's rapidly progressive pulmonary involvement.

Hematologic Toxicity

Patients' hematologic toxic reactions are listed in Table 3. Neutropenia was observed in 95% of patients and during 89.4% (126 of 141) of assessable cycles. Grade 4 neutropenia was seen in 72% (33 of 46) of patients. When evaluated by previous paclitaxel dose, grade 4 neutropenia was seen in 80.8% of low-dose and 75.0% of high-dose paclitaxel

Table 3. Hematologic Toxic Reactions (46 patients)

Variable	Nadir		Grade 3		Grade 4	
	Median	Range	No	%	No	%
Leukocytes, × 10^3/μL	1.3	0.4 to 6.1	24	52	11	24
Neutrophils, × 10^3/μL	0.2	0.0 to 5.7	6	13	33	72
Platelets, × 10^3/μL	195	28 to 549	1	2	0	0
Hemoglobin, g/dL	9.9	6 to 12.4	3	7	1	2
Infection			6	13	0	0

patients. The median duration of neutropenia was 7 days (range, 2 to 28). In only one cycle did grade 4 neutropenia last longer than 7 days. The median nadir for both leukopenia and neutropenia was reached in 7 days (range, 5 to 14).

Febrile neutropenia, defined as fever greater than 38.0°C, related possibly or probably to the study drug, and concomitant with neutropenia (< 500 cells/μL) that required intravenously administered antibiotics and/or hospitalization, was observed in 11 patients (24%) and in 12 of 199 cycles (6.0%). Febrile neutropenia occurred in 27% (eight of 30) of patients and 7% (nine of 121) of cycles in the low-dose paclitaxel group, and in 19% (three of 16) of patients and 4% (three of 78) of cycles in the high-dose paclitaxel group. Grade 3 infection occurred in six patients (13%) and in seven of 199 cycles (4%), but no cases of grade 4 infection or septic death were observed.

Nonhematologic Toxic Effects

Nonhematologic NCI-gradeable toxic effects possibly or probably related to the study medication are listed in Table 4. The most common toxic effects were neurosensory ones (73.9%) and stomatitis (52.2%), but most were mild or moderate (grade 1 to 2). No NCI grade 4 nonhematologic toxic effect was reported. No grade 3 or grade 4 hypersensitivity reactions occurred; one grade 1 and one grade 2 hypersensitivity reaction were reported.

Neurosensory toxicity was observed in 34 patients (73.9%), but only three patients experienced severe (grade 3) neurosensory events. No difference was seen in the incidence of neurotoxic effects between patients previously treated with high-dose paclitaxel (69%) versus those previously treated with low-dose paclitaxel (77%).

None of the skin toxic reactions (rash or nail changes) observed in 20 patients (43.5%) were classified as severe. The most commonly encountered skin reactions included a diffuse macular erythema, acral erythema, and focal erythematous papular rash. Dermatitis occurred in 11 patients (23.9%) and a nail disorder in nine patients (19.6%). This included six (20.0%) patients who had dermatitis and four patients (13.3%) who experienced nail changes in the low-dose paclitaxel group, and five patients (31.3%) with dermatitis and five (31.3%) with a nail disorder in the high-dose group.

Nonhematologic non–NCI-gradeable toxicities were asthenia in 32 patients (69.6%) and myalgia in 22 patients (47.8%). Asthenia was moderate in 16 patients (34.8%) and severe in 10 (21.7%). In the low-dose paclitaxel group, 19 patients (63.3%) had asthenia (nine moderate and six severe). In the high-dose paclitaxel group, 13 patients (81.3%) had asthenia (seven moderate and four severe). Myalgia was moderate in 15 patients (32.6%) and severe in three. There was no difference between the low-dose and high-dose groups (46.7% and 50%, respectively).

Fluid retention occurred in 23 patients (50.0%). In seven patients, it was moderate and in two patients (4.4%) it was severe; both were a combination of edema and effusion. There was no difference between previous paclitaxel dose groups (low-dose 53.3% v high-dose 43.8%). The cumulative doses that preceded severe fluid retention in these two patients were 300 and 500 mg/m^2 (three and five cycles), respectively. Overall, the median cumulative dose to onset of moderate or severe fluid retention was 297 mg/m^2 (range, 88 to 626 mg/m^2). In the low-dose paclitaxel group, the median cumulative dose to onset of fluid retention was 297 mg/m^2 (88 to 626 mg/m^2), and in the high-dose paclitaxel group it was 292 mg/m^2 (272 to 311 mg/m^2). No patients were withdrawn from the study because of fluid retention.

Chronic docetaxel-associated adverse events such as fluid retention, asthenia, and neurosensory/neuromotor events were classified according to previous cumulative paclitaxel dose to learn whether the two taxanes might have additive effects (Table 5). Generally, the percentage of patients who

Table 4. Acute Nonhematologic Toxic Effects

	All Patients (N = 46)				Previous Paclitaxel Dose ≤ 175 mg/m^2 (n = 30)				Previous Paclitaxel Dose > 175 mg/m^2 (n = 16)			
	Total		Grade 3		Total		Grade 3		Total		Grade 3	
NCI Term	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Neurosensory	34	73.9	3	6.5	23	76.7	2	6.7	11	68.8	1	6.3
Neuromotor	6	13.0	–		2	6.7	–		4	25.0	–	
Stomatitis	24	52.2	4	8.7	16	53.3	2	6.7	8	50.0	2	12.5
Nausea	22	47.8	2	4.3	14	46.7	2	6.7	8	50.0	–	
Vomiting	7	15.2	2	4.3	4	13.3	2	6.7	3	18.8	–	
Diarrhea	21	45.7	3	6.5	16	53.3	3	10.0	5	31.1	–	
Fever in absence of infection	18	39.1	8	17.4	12	40.0	5	16.7	6	37.5	3	18.8
Skin/nail	20	43.5	–		14	46.7	–		6	37.5	–	

Table 5. Patients With Adverse Events, Classified by Previous Cumulative Paclitaxel Dose

Cumulative Previous Paclitaxel Dose (mg/m²)	Neurosensory		Neuromotor		Asthenia		Skin		Fluid Retention	
	No.	%	No.	%	No.	%	No.	%	No.	%
0-400 (n = 8)	6	75	0	0	5	63	3	38	5	63
> 400-800 (n = 14)	11	79	4	29	8	57	4	29	8	57
> 800-1,200 (n = 10)	7	70	2	20	4	40	2	20	4	40
> 1,200 (n = 14)	10	71	2	14	6	43	2	14	6	43
Total events	34		8		23		11		23	

experienced an adverse event associated with docetaxel treatment did not increase with an increase in the cumulative paclitaxel dose.

DISCUSSION

This open-label multicenter phase II clinical trial evaluated drug efficacy and drug safety profile of patients treated with docetaxel for paclitaxel-resistant metastatic breast cancer. Paclitaxel resistance was defined stringently, and most patients had significant previous paclitaxel exposure.

The overall objective response rate of 18.1% and the intent-to-treat objective response rate were similar. Previous paclitaxel dose and type of resistance (primary *v* secondary) did not affect the response rate. A higher response rate was seen in the patients who had received paclitaxel by 1- to 3-hour infusions compared with those who had received 24-hour infusions (25% *v* 0%), but this did not reach statistical significance. Activity was seen even in patients with poor prognostic factors, including those with liver metastases, extensive previous therapy, and anthracycline-resistance/exposure.

The results of this study showed that docetaxel is active in patients with paclitaxel-resistant breast cancer and they confirmed the indications of preclinical studies that paclitaxel and docetaxel have only partial cross-resistance in cell lines in which resistance to paclitaxel was induced.[3] The relative differences between the two taxanes in potency and efficacy may play a role in the absence of complete cross-resistance between the two drugs. Docetaxel, for example, exhibits much higher potency than paclitaxel in induction of *bcl-2* phosphorylation, which suggests docetaxel's relatively greater potential for inducting apoptotic death in cancer cells.[13] Whether any specific mechanism of resistance is more important for paclitaxel resistance than for docetaxel resistance is not known. Cells that develop resistance to paclitaxel through mechanisms that involve microtubule processes may remain sensitive to docetaxel if the *bcl-2* phosphorylation mechanism remains sensitive to docetaxel.

Only two reports have been published of phase II trials with patients who had strictly defined paclitaxel resistance. The response rate for docetaxel in our study was comparable to that seen with 96-hour continuous infusion of paclitaxel (27%)[25] and with dose-intensive vinorelbine (25%).[26] In the former study,[25] earlier brief infusions of paclitaxel had failed in all patients. No patient had received 24-hour infusions. The toxic effects of 96-hour paclitaxel in this population were comparable to that seen in our study; overall, in terms of both risks and benefits, the results are equivalent between the former[25] study and the present trial. A 96-hour paclitaxel infusion regimen may not be feasible in all general oncology practices, but it can be accomplished in specially equipped centers.

Livingston et al[26] administered vinorelbine at doses of 30 to 35 mg/m²/wk with continuous granulocyte colony-stimulating factor (G-CSF) support. The patients' median survival time was 33 weeks. Noting the unfavorable pharmacoeconomics of this regimen, the authors do not advocate routine administration of concurrent G-CSF and vinorelbine in this setting.

Moderate to severe neutropenia was common in our study, with neutropenic fever the most frequent major adverse event. Because of the incidence of neutropenic fever (in 23.9% of patients, 6% of cycles), either a lower dose of docetaxel (75 mg/m²) or the use of prophylactic colony-stimulating factors (granulocyte-macrophage-CSF or G-CSF) or antibiotics (ciprofloxacin or levofloxacin) should be considered in patients who have been heavily pretreated or who have risk factors of severe neutropenia (such as extensive previous radiation therapy and known inability to tolerate myelosuppressive treatment).

The incidence of neurosensory toxicity (of any grade) was higher than is usually reported with single-agent docetaxel, but the incidence of severe neurotoxicity was comparable.[1,2] In contrast, the incidence of hypersensitivity reactions, fluid retention, and skin toxicity related to previous paclitaxel exposure was lower than those initially reported.[1-2,27] However, in this study, patients on the docetaxel regimens had been premedicated with dexamethasone, which clearly decreased or ameliorated these adverse events.[2,27,28] Recently, a 3-day dexamethasone regimen was reported to be as effective as a 5-day regimen in ameliorating docetaxel-induced toxicity, with less severe steroid-related side effects.[29]

In summary, the results of this multicenter trial showed that docetaxel is active in patients with paclitaxel-resistant breast cancer. The response rates observed were comparable

or superior to those seen with other salvage therapies. Adverse events were similar to those seen in previous docetaxel studies. There was no evidence for additive cumulative toxic effects of the two taxanes. Although the results of this trial demonstrated the absence of complete cross-resistance to docetaxel in paclitaxel-resistant breast cancer patients, they do not imply absence of cross-resistance in patients who may have been treated with paclitaxel for other neoplastic diseases.

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The House Magazine of the Cancer Patients Aid Association

Cancer Care

Sing for Hope Sing for Cancer.

March 1999

Vol 3

DIS-18

Editorial

This issue of Cancer Care is dedicated to children with cancer. This is the area where there is much more hope of survival after cancer. There are statistics to prove that there are thousands of adults who suffered from cancer in childhood who are now leading normal and healthy lives.

Some children do succumb to this dreaded disease but this is due to the site of the cancer and how late it has been diagnosed. Immence progress has been made in the treatment of cancer and we are sure more and more children will survive. In India, the statistics show, more children die of malnutrition and other communicable diseases than of cancer.

Not that this is any consolation. CPAA is aware of the pain of the loss and the despair felt by the parents when a Sunaina or a Jigar who were responding so well to chemotherapy and were fighting so gallantly, suddenly lose the battle.

Hope is eternal. We also Hope to find the answers one day.

Sarla Kolhi

IN THE MAIL

Madam,
I have read with interest the write up which appeared in EXPRESS WEEK dated 9/05/98. I am indeed touched by the humanitarian work you are carrying on for the cause of cancer patients, particularly the poor. May god bless you and all your co-workers in your noble venture.

E.F.Noronha
Bangalore – 560 041

Respected Madam,
I take this opportunity by thanking CPAA for giving me such a wonderful opportunity to serve as a volunteer for distribution of Rose, gifts etc. to Cancer Patients on Cancer Rose-Day the 22nd September.
22nd September - Cancer Rose Day – Rose Distribution Day – a day of silver lining for CPAA a day to remember for cancer patients young and old, when they have been conveyed through Roses, Toys, gifts etc that we, the citizen of Mumbai CARE for them. And of course a day to treasure for us.

Shri Vasant B. Dalal
Andheri (West)
Mumbai – 400 058

Respected Madam,
I, the undersigned, R.M.Agrawal, grand father of Payal Agrawal, who is aged 17 years, at present boarding at 'Borges Memorial Home, Bandra, and undergoing treatment at Tata Memorial, beg to express my heartfelt gratitude, for your selfless services rendered to the attendants of patients, coming from various parts of not only India, but abroad.
The work your association does is really appreciated. To add to the glory of the association, your ever smiling and cheerful handling, politeness and very sympathetic talk, no doubt reduces the tension of the needy persons like us.

R.M.Agrawal
Bhillai – 490 001.

Dear Ms. Alka Kapadia,
Couple of years back, my wife and I took an Insurance cover promoted by Bombay based Cancer Patients Aid Association. In December 1997 my wife had to undergo hysterectomy for a moderate adeno carcinoma of endometrium, at Breach Candy Hospital Bombay. This took me for the first time to the office of C.P.A.A. to lodge with them my wife's Insurance claim. The claim, in toto, was settled in record time of 10-15 days! Experiencing the service-orientation of C.P.A.A. one gets highly motivated and enthused. I hope and pray C.P.A.A. continues this good work and pursue their cause of serving distressed humanity.

A.N. Sarin
Hyderabad – 500 034

International union against cancer

Viji Venkatesh and Alka Kapadia of CPAA Mumbai, attended the UICC Congress at Rio in 1998. It was an opportunity for Viji to interact with the other members of the COPES Steering Committee. Viji who is already a UICC member, was invited to join the Steering Committee from August 1998 to December 1999.

COPES (Campaign, Organisation, Public Education and Patient Services) Programme is committed to the UICC member organisations and to the establishment of a worldwide network of collaborating voluntary cancer control agencies; to assuring that they are efficiently organised to effectively carry out their mandate in cancer control and to the provision of service to cancer patients.

The main objectives of this programme are, to facilitate communication and information sharing between voluntary cancer societies throughout the world, as well as to initiate and support cancer societies by providing training opportunities for their staff and volunteers, particularly in the area of public education and patient services.

At Rio, one of the first decisions was to set up a website specifically for the COPES arm and make it accessible to all groups and agencies working for the cause of cancer care the world over ... this website will be a store house of informational resources and it is the responsibility of each member to see to it that cancer organisations of the geographical areas they represent are able to benefit from this exercise.

Each member of COPES has given the feed back and input as to the nature and volume of demands from each country and now are busy gathering information as to what are the existing resources available and how best to implement an effective learning and sharing procedure — whether it is providing practical assistance to patients, setting up specific support programmes or educating the youth and community at large. Everyone working in this field is involved in one or more of the above areas of cancer care. CPAA also successfully developed and implemented quite a few effective and result oriented community programmes which will serve as wonderful models for others to learn and adapt from.

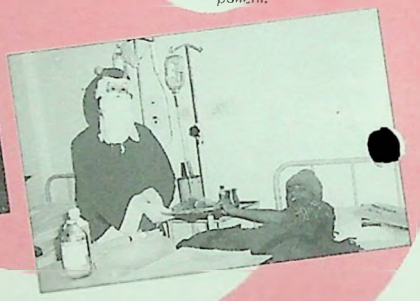
Seen at UICC Meet at Rio from left: Alka Kapadia and Viji Venkatesh with Dr.Dinshaw, Director Tata Memorial and Dr.and Mrs. Prafulla Desai

Bringing a smile to those in pain

Another look at Patient Care

One of our prime channels to alleviate pain and assist cancer patients is to give free aid and disburse medicines. This in effect means looking into the family circumstances to decide how helpful we can be in each case. In addition we at CPAA believe, that a disease like cancer hits not only the body but the mind and soul of not only the patient, but the entire family ! Hence over the years we have begun associating closely with activities that will bring some moments of cheer to the patients. CPAA is nationally committed to this charter, and the enunciation is in different ways in the different branches. Part of this effort is observed through Rose Day on September 22 when CPAA visits hospitals and patients and extends an invitation to as many volunteers and celebrities to join the teams to spread the message of Care and Hope.

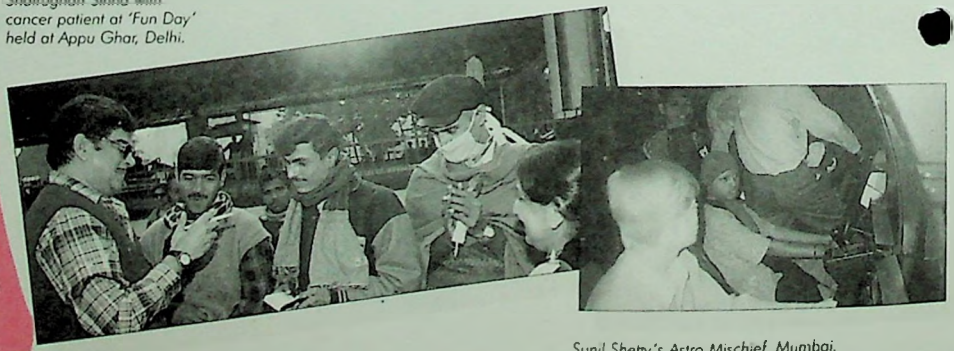
Christmas Party at Ernest Borges Home



Santa Klaus at Inlaks Hospital Pune, cheering a patient.

'Patients Day-Out' was held at a 'Fun Day' at Mumbai and Delhi when patients mixed with celebrities, were given gifts and treats. A wonderful time was had by all. X mas father visited the Ernest Borges Home in Mumbai and Inlaks

Shatrughan Sinha with cancer patient at 'Fun Day' held at Appu Ghar, Delhi.



Sunil Shetty's Astro Mischief, Mumbai. A day in space for children with cancer.

Volunteers of CPAA with Kiran Bedi on Rose Day at Delhi

The actress Ranjita enjoying a moment with children at Inlaks hospital, Pune.

Shobha De and Shashi Kapur with Mr. Y.K. Sapru, Chairman CPAA, at a Press Conference on Rose Day.

Tina Ambani at Children's ward in Mumbai on Rose Day

Cancer Patients Aid Association gave medicines worth Rs.17.75 lakhs in **Mumbai** alone during January to December 1998. Other help given in kind is in the form of rations, clothes, nutritional supplements, toys, wheel chairs, educational scholarships, prosthesis, ambulance service etc. **Delhi** chapter which was started in 1980 was able to give aid worth Rs.3,77,822.00 to 755 patients, out of which 324 were new cases taken up in 1998. **Bangalore** donated medicines worth Rs.2,15,717.00 in 1998 to 420 patients. Scan charges, ambulance services nutrients etc. worth Rs.45,000.00 were also given. **Pune** was able to aid 379 people in 1998 with medicines, counselling and care.

Hospital, Pune, to give gifts to the young patients. Little patients had a wonderful time at Sunil Shetty's Astro Mischief in Mumbai.

Our efforts are aimed at making the patients feel that they are like other normal people who also fall sick and are not pariahs to be shunned by society.

Child patients enjoying themselves at Fantasy Land, Mumbai

Film Star Dimple Kapadia with children suffering from cancer on Fun Day.

A look at some stars CPAA is proud of

In keeping with CPAA's philosophy of Total Management, we are involved with patients from diagnosis and awareness to rehabilitation and being productive citizens of the nation. We believe in self-worth and self-respect to be maintained, without which life is not worth living. CPAA is happy to profile some of the people we have been able to help and work with.

Vidhi Doshi, 13 years old, a case of relapsed Acute Lymphoblastic Leukemia now completely cured after a Bone Marrow Transplant at the Royal Marsden Hospital, U.K. She is the first beneficiary of our tie-up with British Airways 'Donate your miles Scheme'. She and her father were given free tickets for her treatment abroad by British Airways. We helped her with a list of Charitable Organisations in U.K. along, with an appeal addressed to each of them for financial assistance.

Sangita Bhise, 14 years old, a case of Retinoblastoma hailing from Kolhapur, undergoing treatment at TATA MEMORIAL HOSPITAL (TMH). In addition to supporting her treatment, we helped rectify her gross disfigurement by organising an artificial eye implant for her which has made her look really normal – much to her joy and that of her family.

Padmanabhan Thevar, 17 years old, a case of Hodgkins Disease now completely cured after treatment in TMH. We fully supported his treatment (adopted him) and have raised funds to pay for his Computer fees at NIIT. He's doing very well – being an intelligent and hardworking young boy. He's simultaneously doing his graduation in Commerce as well.

Jayshree Rajput, 23 years old, daughter of our expired cancer patient. We got her enrolled into a beautician's course and got her a job subsequently. When she was confident of her experience and expertise, we helped raise funds for her to set up a beauty parlour in a place on rent. No we are trying to get her help from the Nehru Rozger Yojna to set up a beauty parlour on a permanent basis.

Chamundeshwari Patil, 25 years old, completely cured of Hodgkins disease after treatment at TMH. We supported her treatment, fixed up accommodation at a Working Women's Hostel for her, gave her a job as Administrative Assistant,

raised funds to pay her MCA course fees at NIIT. After 6 months, she went back home to Raichur. Had the fees transferred to NIIT's branch in Raichur. She is now just married and is setting off to [redacted] on January 5th 1999 and will join the NIIT there.

Sudhir Nikharge, 26 years old, a case of osteosarcoma from TMH. He has undergone a total knee replacement surgery. The prosthesis cost a whopping Rs.5 lakhs. We raised the funds through countless appeals to Trusts, Commercial Organisations, media and Publications and the general public. He is a Chartered Accountant and we have fixed up a job for him with a foreign bank – but he insists he'll join only after he feels cent percent restored back to normalcy.

Irfan Razak, 27 years old, a completely cured case of ALL from BYL Nair Hospital, hailing from Surat. In addition to all the medical, dietary and Vehicular help we gave him, we also successfully socio-economically rehabilitated him. We have raised funds to partly pay for an Autorickshaw for him. The balance money was arranged through a bank loan. He is now a full fledged autorickshaw driver and is very happy with his success.

Manoj Thakker, 40 years old, a case of cheek cancer caused by constant chewing of gutka treated at TMH and now totally cured. He was referred to us post – treatment. Helped raise funds to pay off his pending medical bills, provided extensive emotional support, (as his wife and child had deserted him after his cancer diagnosis) helped him with basic sustenance requirements, got him a job at our Rehabilitation Centre in the Marketing Section, since he had a background in this, prior to his illness. We arranged a Coca Cola Booth at Andheri Lokhandwala Complex for him and he is, doing very well now.

Urmi Mody, 6 years old, a cured case of ALL from TMH. This friendly and chirpy child is a real treat for the eyes. CPAA has supported her entire treatment. Seeing her extrovert nature and good communication skills, CPAA helped her get a role in a TV Serial, much to her delight.

Madaswamy Konar, 24 years old, a case of rectum cancer from BYL Nair Hospital. CPAA supported his entire treatment. He has to use colostomy bags lifelong and CPAA is supporting him for the same. We have raised funds for him to get enrolled for a Computer Course.

Jigar Waghela, 5 years old, a case of ALL from B J Wadia Children's Hospital. Jigar, the heart-throb of all who set eyes on him, was totally supported by CPAA for his treatment. Initially, he was responding excellently to the treatment. Due to this, plus the fact that he was a cute and even – tempered child, he was selected as our Rose Day 'mascot' for 3 consecutive years. Unfortunately, he suffered a bad relapse in early 1998 and expired just a week before Rose Day '98. CPAA was of emotional and practical support to his heart – broken parents. CPAA arranged for Rs.8000/- towards the last rites to bid him a dignified farewell. We are also in the process of getting Jigar's father a job.

Santosh Kumar, 4 years suffering from small round cell and tumours of the Pelvis has been looked after by CPAA since a year and may have to undergo surgery. His mother Pappama who has another three children, has tremendous courage and indefatigable fortitude. We salute her immense optimism and wish Santosh Kumar, all the best.

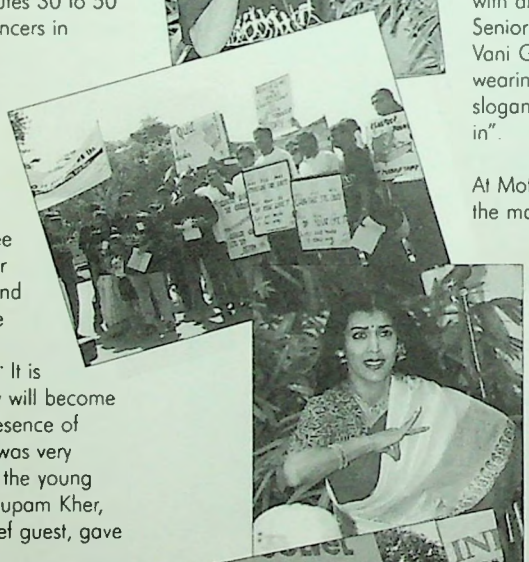
World No Tobacco Day

The Perfect Opportunity to create awareness of the harm caused by tobacco consumption

World No Tobacco Day is a national activity taken on by all branches of CPAA, who use different methods and means to capture the attention of the relevant audience — the impressionable youth.

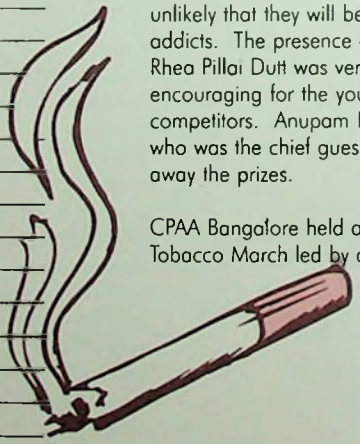
The primary objective of CPAA's awareness drive in May is to bring the scourge of tobacco to light. This allows for attention to one of the primary causes of oral cancer — which constitutes 30 to 50 percent of all cancers in India.

In Mumbai an art competition was held for children on this day. It was astounding to see the depth of their understanding and awareness of the great harm that tobacco causes. It is unlikely that they will become addicts. The presence of Rhea Pillai Dutt was very encouraging for the young competitors. Anupam Kher, who was the chief guest, gave away the prizes.

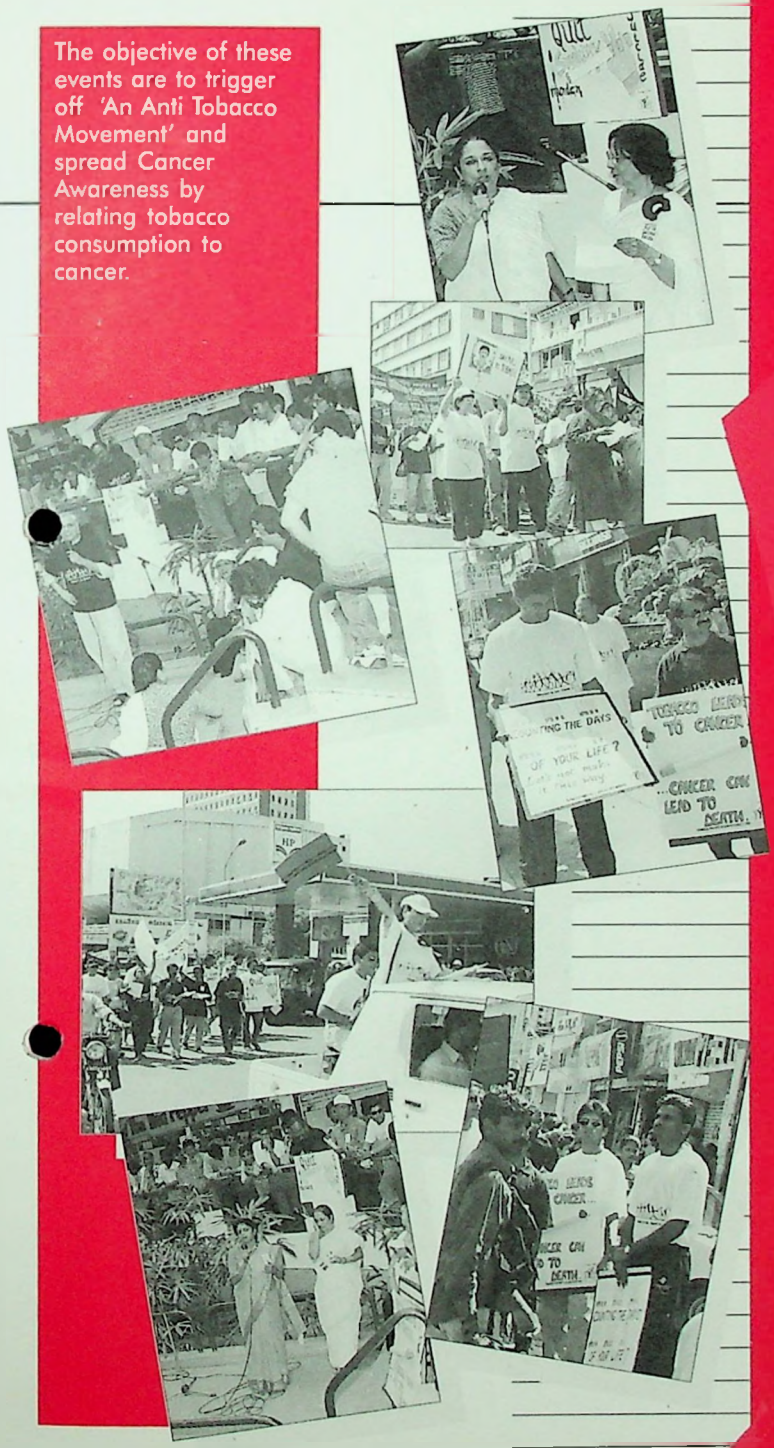


CPAA Bangalore held a No Tobacco March led by a jeep with Geeta Gopalakrishanan belting out anti-tobacco slogans. Cricketers like Rahul Dravid and Srinath and veteran cricketers like Brijesh Patel, Syed Kirmani, marched with anti smoking placards. Senior Artists Vasudev, Arakal, Vani Ganpathy marched wearing T-shirts with the slogan "Tobacco is out, you're in".

At Mota Royal Arcade where the march ended, questions of the public on cancer were answered by Oncologists. What kept the crowd in place were special songs on tobacco specially penned for the occasion.



The objective of these events are to trigger off 'An Anti Tobacco Movement' and spread Cancer Awareness by relating tobacco consumption to cancer.



Tobacco Statistics

Tobacco kills nearly 10,000 people ever day. According to the World Health Organisation it is predicted that over 500 million people currently alive will be killed by tobacco.By the year 2020, according to current trends, seven million of the tobacco related deaths out of the ten million that are being projected, will be occurring in developing countries like ours. Two million Indian children get addicted to tobacco.

Did you know that...

Tobacco causes 10 lakhs deaths annually in India. ● One tobacco-related death occurs every 10 seconds. ●Tobacco contains over 4,000 different chemicals, 43 of these are proven carcinogens.● Passive smokers are at a higher risk of getting cancer.● Cigarettes and beedies kill one in every five of us.● 500 million people alive today will be killed by tobacco. The widespread usage of tobacco in its various forms is responsible for the fact that oral cancer is the no. 1 cancer among Indian males.● 6 billion cigarettes are smoked annually.● Heavy smokers who smoke more than two packs a day have a death rate which is 140 percent greater than non smokers. ●The relaxed feeling felt by smokers is a pseudo-relaxation. In fact, nicotine causes an increase in the pulse rate and blood pressure.

Childhood Cancers

Dr. Rakesh Mittal, M.D.: D.M. Consultant, Medical & Pediatric Oncologist

Pediatric and adolescent cancer cases represent a small proportion of world wide cancer burden. In western countries, about 10.4% of all deaths in children are from cancer and it constitutes about 2% of all cancer cases. The Indian figure is not very clear. But it is not a major cause of death. In our country diseases like diarrhea, malnutrition, and infections constitute major causes of death. The exact magnitude of childhood cancer in India is not exactly known because there is no nation-wide survey. But because of sheer volume of pediatric cases, the number of children suffering from childhood cancer is enormous.

Causes of childhood cancers

A question that often arises in the minds of parents when their child is newly diagnosed with cancer is "Did this happen because of something I did or passed on to my child ?" But generally it is not so. The percentage of childhood cancer that are caused by a clearly inherited predisposition or significant environmental exposure is very low. There are no known causes of cancer in most of the cases. The factors, which have been implicated in the causes of childhood cancer are certain viruses, radiation, chemicals, and genetic factors.

Types of childhood cancers

Childhood cancers can broadly be divided in to two types of cancer:

Hematological malignancies
Non hematological malignancies

Hematological malignancies:-

There are two main types of hematological malignancies. Leukemias (blood cancers). In which we have acute and chronic type. Lymphomas. They are Hodgkins disease and Non Hodgkins Lymphomas. Among leukemias the most common type is acute lymphoblastic leukemia, which constitute about 70% of all childhood leukemias. The other type is acute myeloid leukemia, which is bout 20-25% of all leukemias. Among lymphomas most common are high grade Non Hodgkins lymphomas.

Non hematological cancers or solid cancers:-

Solid cancers of childhood are the cancers of various organs like brain, liver, kidney, bones, muscle, adrenal glands, and testis or ovary. Among solid cancers the most common are tumors of brain (brain tumors) kidney (Wilms tumor), muscles (Rhabdomyosarcomas), and bones (Osteosarcoma) and germ cell tumors of gonads.

In children, leukemias, brain tumors, and lymphomas are the most frequent tumor types. Hematological malignancies constitute about 1/3 of all cancers while rest are solid tumors.

Differences between childhood and adult cancer in the hematological cancers

The main difference is that among leukemias, the predominant type in children is acute leukemias while in adults it is chronic leukemias (CML,CLL). Among lymphomas, in children the predominant type is high-grade lymphomas while in adults it is low-grade lymphomas.

Among solid tumors, the main difference is in the type of tissues involved. In adults it is predominantly squamous cell carcinoma (superficial), while in children it is mesenchymal cells (deeper cells). The other major difference seen is that in children the effect of environment factors like smoking, diet, or pollution is not seen. The effects of genetic factors are more in childhood cancers.

The early warning signs seen in adults are not seen in children. In children the signs and symptoms of malignancy are common symptoms like fever, headache, lymph node enlargement, weight loss etc. Hence there is no role of screening for childhood cancers. The childhood cancers are more aggressive than adult cancers and this is the reason they are more responsive to chemotherapy, hence their survival is better.

Signs and symptoms of childhood cancer.

As mentioned above it is difficult to diagnose childhood cancers in its early stage because the signs and symptoms of childhood cancer are relatively nonspecific and may mimic a variety of other, more common childhood disorders. For a pediatric oncologist, the index of suspicion for a diagnosis of cancer is high, while for primary care physician, the opposite is more often true.

Management of childhood cancers.

Management of childhood cancers is a multimodality treatment strategy. We have three modalities of treatment for all cancer patients namely, surgery, radiotherapy, and chemotherapy. For different malignancies, the various modalities are combined in an appropriate manner depending upon the sensitivity of malignancy to a particular modality. For hematological malignancies the main modality of treatment is chemotherapy while for solid cancers normally all the modalities are combined.

Results of treatment of childhood cancers.

Since the introduction of chemotherapy for childhood leukemia nearly 50 years ago, the prognosis of childhood cancer has improved dramatically. The long-term survival, which was less than 10% four decades ago, is now in the range of 60-70%. Apart from advances in the field of chemotherapy, surgery, and radiotherapy, other factors which have made a difference in the increased survival are improvement in the supportive care and introduction of newer methods of diagnosis. The most notable difference can be seen in Acute Lymphoblastic Leukemia, Hodgkins Disease, Non-Hodgkins Lymphoma, Wilms tumor, Rhabdomysarcoma, Germs cell tumors and Bone tumors. In some childhood cancer 5 years survival may be called as cure, while in others there may be relapses even after many years. The malignancies where treatment has not made much impact are Acute Myeloid Leukemia, and Neuroblastoma. The childhood malignancy is no more a universally fatal disease. If diagnosed early and given a proper treatment for sufficiently long time then we can easily cure it. Interestingly, in western countries there is a large number of adult population who suffered from one or other type of childhood cancer and are leading a normal life. In fact in the management of childhood cancers, now the main concern other then curing the disease is to prevent long term complications. Because these children when cured of their cancers are going to lead a normal adult life, and there should not be any stigmata of their childhood cancer on their adult life in the form of any physical or psychological disability.

Future of Childhood malignancies.

The future of the cure of childhood malignancies looks very bright. What is needed is refinement and better utilization of available modalities of treatment. Then there is need to look for new innovative methods of treatment. Most notable in this are gene therapy and immunotherapy. Time is not far when childhood malignancies will no more be considered as a dreadful disease. The treatment will be like that of any other childhood disease.

Q & A on Cancers in children

Bright and beautiful Sunaina - a victim of Medula Blastoma

Do children really get cancer ?

Yes, although the types of cancer which occur in children are rather different from those which occur commonly in adults. Altogether, about one child in 600 will develop cancer before the age of 15 years. Of the cancers which occur, about one third are leukemia. The next most common are the brain tumours, but cancer can occur in any part of the body. Cancer can occur at any age; very occasionally the tumour is already present at birth.

What causes childhood cancer ?

Very little is known about this. Unlike adult cancers, there is no clear evidence that they can be caused by environmental agents such as chemicals. In the past, some may have been caused by excessive exposure to x-rays but this is unlikely to happen nowadays as doctors are aware of the possible hazards and take appropriate precautions.

Cancers themselves are not usually hereditary. (The only important exception to this is retinoblastoma, a type of eye cancer, which is often inherited.)

What are the symptoms of childhood cancer ?

These depend mainly on where the tumour is situated. Brain tumours often cause persistent headaches, vomiting or dizziness. Other tumors appear as a lump, for example, in the neck or in the abdomen. Often, there is no pain and, even when pain is present, it is rarely severe. Although there are many ways in which cancer can present, there are often alternative, less serious explanations for some unusual symptoms. However, if you are in doubt or worried, take the child to your doctor for an examination. If necessary, tests should be arranged or the child referred to a specialist or hospital.

Can anything be done for childhood cancer?

There have been many important discoveries made in the treatment of cancer in the last few years. As a result, many forms of childhood cancer can now be cured. Some forms of cancer are more likely to respond to treatment than others. With some types, nearly 100% of cases are cured with appropriate therapy. Overall, more than half the children who have cancer are cured, and can look forward to a normal active life.

What is the treatment?

This varies according to the type of cancer, its site within the body and the extent to which it has spread to distant parts. The three main kinds of treatment used are surgery, radiotherapy (x-ray treatment) and chemotherapy (Treatment with anti-cancer drugs). With some localised tumours, surgery alone may be all that is required to provide a cure but most cases will require radiotherapy or chemotherapy or both. Radiotherapy takes a few weeks to complete. Chemotherapy is given intermittently, over a period varying from a few months to two years. While on chemo-therapy, children will be able to take part in normal activities.

Are the children actually cured?

Despite what some people believe, cancer can be permanently cured. There is an increasing number of adults around nowadays who are perfectly healthy and normal and have had cancer in childhood. They are able to work normally, marry and have children. It is extremely unlikely that they will pass on cancer to their own children.

A look at 1998

CPAA's Diagnostic Camp Statistics

1987-1998 (MARCH)

Total number of camps held	— 2,183
Number of Individuals screened	— 78,315
Males	— 53,862
Tobacco Users	— 43,200
Females	— 24,555
Tobacco Users	— 4,780
Suspected cases	— 8,466
Detected	— 84

5 Point Target for Awareness & Counselling

- Volunteer Service at TMH
- CPAA Website
- Head & Neck Group Sessions at TMH
- FDA Meet
- Ambulance Services

Cancer Patients Aid Association's Awareness and Education Programmes have started to cater to a new group...children and young adults. A frightening increase in tobacco consumption trends in this age group and relentess targetting of these youngsters by the tobacco companies has left us with no option but to reach out to these youngsters who are being duped into making uninformed choices.

Activities

- Awareness Material brought out:
  - -Posters
  - -Pamplets
  - -(BSE, Warning Signs
  - -Information on CPAA)
- CPAA Website
- Ernest Borges Home Play Group
- Wadia Hospital Support Group
- Head and Neck Support Group
- CPAA cell at TMH
- Naigaum /Airoll spade work
- Head & Neck Oncology Conference Workshop.

Reaching out to young adults has been worked out with help from the NSS Programme Officers Training project of the TISS. Access to students has not been a problem and regular Awareness Programme are being held in colleges all over the city. On another level CPAA has also been working on a project which will create cancer and tobacco awareness in secondary school children.

At TATA Hospital, Wadia Hospital and Ernest Borges Home, our patient related programmes are well attended and appreciated. Volunteers Deepali Kapoor and Urmila Ausekear run a weekly counselling cell for Head & Neck patients, an important component of the Support Group, and Deepali also runs another weekly session for patients referred to the Palliative Clinic (Both of these at Tata Hospital).

It has to be mentioned that the CPAA staff from the Diagnostic and Policy Depts are very sincere volunteers for the Tata Hospital counselling desk and are doing a tremendous job. An informal workshop on counselling and listening skill was organised for the CPAA staff. Deepali Kapoor (herself a trained professional counsellor) conducted the one day session. With more such sessions CPAA staff will be equipped with all the necessary skills...they already have the most important one...commitment.

DIAGNOSTIC CENTRE

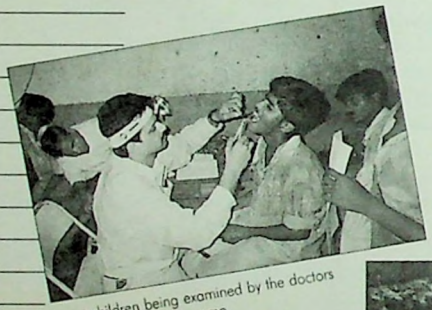
MUMBAI

TOTAL NO. OF CAMPS/CLINICS/CIPS	: 259
TOTAL NO. OF MALES SCREENED	: 3890
TOTAL NO. OF FEMALES SCREENED	: 3459
TOTAL	: 7349
TOTAL FOLLOW UP CASES	: 1712
DETECTED CASES OF CANCER	: 3
TOTAL PAP SMEAR TAKEN	: 2735

AWARENESS LECTURES / CAMPS

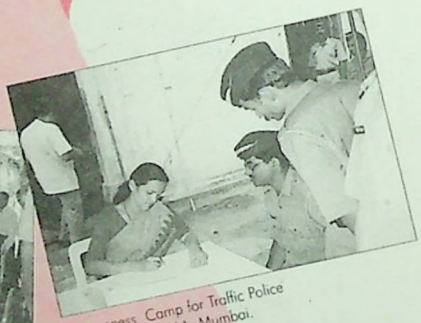
Awareness lectures were held in

Lonavala for the Cadets, Sailors and Sailor's wives..this will be Followed by a camp there (INS SHIVAJI) in March.
Matunga, for the Central Railway employees Hindustan Mills
Patel wadi in Jogeshwari (350 families-open air lecture 9 pm 10 pm...incredible audience)
Trainee Volunteers from SNDT Cosmopolitan Education Society Art College Andheri Gurunanak College Sion-Kollwadas NAL, ISRO, BEML
OFFICES IN BANGALORE
HAL OFFICERS WIVES, BANGALORE



Street children being examined by the doctors during the Awareness camp

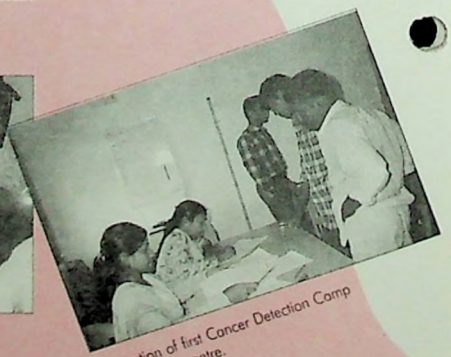
Line for Registration for a free Detection check-up camp in Mumbai



Awareness Camp for Traffic Police organised by CPAA, Mumbai.

Viji Venkatesh at an awareness lecture at a Camp for street children

CPAA, Mumbai organises Awareness Camp for street children



Registration of first Cancer Detection Camp at Pune's new centre.

PUNE

- Total No. of Patients given free medical aid — 379
- Total No. of Free Cancer Detection Camps held — 22
- Total No. men checked — 282
- Total No. of females checked — 598

Dr. B.S. Srinath accompanied by the medical staff of Bangalore Institute Oncology

Shreya - the gutsy warrior

Shreya is 5 ½ years old and the only child of middle class parents. Looking at them, one is struck by the happy picture they make but when one talks to them, one realises the unified courage they radiate —a courageous family indeed !

2 ½ years ago, when Shreya was only 3 years old, she was diagnosed as having Acute Lymphoblastic Leukemia – a common, but curable childhood cancer. The parents brought her to the Bangalore Institute of Oncology, where she has been taking treatment for the past 2 ½ years and is presently free of disease.

Today Shreya is a smart, confident, poised child, excellent at her studies (She stands 1st in class) and very popular with everybody. This has been possible only because of the considerable help and support that she has received.

Shreya with Dr.Ramesh at the survivor's Meet organised by BIO

First and foremost from the parents – they have borne her illness with exemplary courage and equanimity; never have they lost hope in their child or their doctors. Secondly, from the hospital and Physicians – they have been totally supportive of Shreya and her family. Thirdly, and very importantly – various individuals and organisations like CPAA have come forward to help her. Although this is a curable disease, it is very expensive (financially, emotionally and physically). Only the presence of a very strong support system can ensure that the patient completes the prescribed treatment. Lastly and most importantly – Shreya herself, has been a model patient, taking the treatment with a maturity far beyond her years. Apart from a little nervousness about the invasive aspects of treatment she bore it all very well and jumped back to her normal self within 2-3 days of treatment.

Shreya and her family are an inspiration to all of us at the hospital, the staff, the doctors and mostly to other patients in the hospital.

Dr. Nalini Rao,
Dr. Shekar Patel

Bangalore Institute of Oncology (BIO) observed the 10th anniversary of its establishment in a unique way by inviting over 300 survivors of this dreaded disease to prove that life is possible after cancer.

It was wonderful to see the doctors, who are always seen as serious fighters of the disease, as entertainers who sang and danced helped by the Nursing and Technical Staff of this premier institution.

The objective of this innovative programme was to reiterate the fact that...

Cancer is curable.

Cancer need not be deadly.

Cancer is like any other disease which can be controlled and cured.

Cancer patients need acceptance by friends and relatives — not their pity.

Reaching Out : To each a different tune

CPAA has tried to reach out special segments of one community with a focussed appeal. The objectives are two fold.

To expand the reach and spread awareness

To generate funds for the cause.

Since CPAA is not funded by any agency, foreign or local — it has to continually raise funds to meet its objective of Total Management of Cancer.

The challenge in raising funds is to take up events which are different, innovative and give value for the money expended by sponsors as well as the audience. Our biggest event in 1998 was the Live Antakshari by Annu Kapur and Pallavi Joshi. The event was held in Mumbai and Bangalore and was immensely popular and successful in both places.

The great energy and charisma of Annu Kapur, his generosity in doing the shows free, the fairness and sincere effort of Mrs. Kapur at the auditions, all went to make a

Prasad Bidapa and Kalpana Kar at the Press meet organised by CPAA.

Sharing a joke at the press conference. Prasad Bidapa, Anu Kapur, Arundhati Nag Rao with Director CPAA, Bangalore

tremendous show.
Mumbai, a great metropolis, with a tradition of charitable events also held Ila Arun Show and organised a celebrity Dinner. Mrs. Birla who was the chief guest donated Rs.1 lakh to the house. We must profusely thank the celebrities who participate fully in all our functions thus making our events scintillating and glamorous.

CPAA Delhi organised two concerts with the co-operation and support of Mr.Arun Goyal at the Essex farms. Anup Jalota and Brian Silas held the audience captivated with their melodious music. Although from two different streams, they are appreciated

Fund-raising and Awareness through competitions like painting story-writing etc are held by all CPAA branches Delhi has been able to raise over 7 lakhs through such drives.

Shobha De talking of her involvement with CPAA at the opening of Close-Up Antakshari in Bangalore.

Amitabh Bachchan and Jackie Shroff at the Ila Arun Show.

Crowd responding to Annu Kapurs magic.

Desert Dhamaka of Ila Arun in aid of CPAA

A Helping Hand

Tina Ambani at CPAA's Rehabilitation Centre

Cancer Patients Aid Association's Rehabilitation Centre in Mumbai is becoming a centre of activities for cancer patients in remission and their families as this is one place where a helping hand is available for everyone.

Like all the other Divisions in CPAA, the Rehabilitation Centre is also self-sufficient and manages its finances independently.

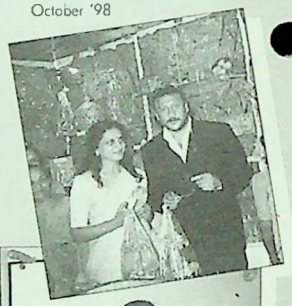
Our designer stationery and terracotta items were exhibited and sold at various outlet including Oberoi Hotel, Aakar Art Gallery, Concern India Foundation, Sydenham College etc. The Society Collection Exhibition at Mumbai and Pune is where our products are really appreciated and selllike hot cakes.

A big thank you to IOC Pumps for allotting stalls put up by Coca-Cola for our patients.

CPAA also arranges to take out rehabilitation patients to all our functions such as Fantasy Land Picnic and X mas party at Oberoi and also to Annu Kapur's Antakshari. It is really wonderful to see the patients.

enjoying these little treats. Our patrons and well-wishers Mr.Madanlal Dalmia and Mr.B.J.Sanghvi distributed Diwali gifts and Bonus to 100 patients and relatives at CPAA's rehabilitation centre.

Jackie Shroff at the Society Collection Exhibition at Pune in October '98



Madanlal Dalmia and B.J. Sanghvi distributing gifts and bonus to some of the patients and their relatives who are under training at the centre.

Activities Report for the period 1ST Jan '98 To 31ST Dec'98

New Patients/Relatives Adopted	30
Total No. of Patients Helped	100 per month
Ration Distributed to	1,331 patients
Total Rations Distributed (Wheat, Rice, Milk Powder, Dal etc)	5,500 kgs
Patients Wages	Rs.12,50,000
Patients Education & Vocational Training	Rs. 2,50,000
Aid given to Patients (Medical, Conveyance, Diet etc.	Rs. 2,15,000
Patients given Breast Prosthesis	35 cases

The Press Says...

Corporate Giants add weight to tobacco drive

The campaign to spread awareness about cancer has received a shot in the arm with several Indian companies coming forward with financial assistance. In a step which could go a long way in controlling cancer as a disease in India, the Cancer Patients Aid Association (CPAA) has come up with a major project titled "Prevent Cancer Epidemic India 2010". They will be aided by some Indian companies, non-governmental organisations and advertising agencies. Taking the lead is Rs.1,000 crore group Gujarat Ambuja Cements Ltd., (GACL). A special cell is being created in the CPAA for educating children in schools and colleges against the ill-effects of gutka and smoking. Youngsters are the primary target group since a recent study showed that over 80 percent cases of gutka consumption starts during the teens. Stating that his organisation is keen to keep up a continuous campaign, Y.K. Sapru founder chairman of CPAA said " With three million cancer patients and another sixty thousand added every year, we are already way behind in managing this epidemic. This is our last chance to protect ourselves from the powerful international lobby and the local gutka and paan masala lobby. It's time cigarette companies pay towards cancer care."

The Bombay Times - 20th May 1998

No bars on health care

Deputy Inspector-General (Jails) Ashok Kininge says "Abstinence has to come from within. The prisoners must realise that such habits can cause serious harm. I am going to introduce such camps in all jails because health management there is very important.

CPAA has conducted such camps in Thane and Arthur Road Jails. An awareness lecture precedes the camp, followed by another camp six months later.

Midday
27th May 1998

Saying it with a rose

The Cancer Patients Aid Association is a voluntary organisation helping cancer patients since 1969. The Bangalore chapter was started in 1994, but to date, the CPAA has been able to reach out to only 1 per cent of the 6 lakh cancer patients in India. "We believe in the total management of cancer — free medication, counselling, awareness, detection and rehabilitation," said Sarla Kohli, regional director of CPAA. "Many patients have found jobs through CPAA. Children of patients who have succumbed to the disease have been placed in families and children with cancer are given medical aid," she added. CPAA has also tied up with British Airways to send children abroad for treatment.

Bangalore Times
31st July 1998

Celebrating Life

The Cancer Patients Aid Association (CPAA) an independent charitable organisation which has been working in Delhi since 1980, organised a day out for cancer patients at the Appu Ghar. Bhupi and Sanjay Raina entertained patients with a special programme while Shatrughan Sinha, Shovana Narayanan and Manpreet Brar mingled with the special guests for the day.

DELHI TIMES - The Times of India - 30th December 1998

They sang their hearts out

The music soaked evening when the lawns, in Manipal County overflowed with people and lights shone on the hugely popular hosts of Close-Up Antakshari, was the culmination of months of hard work and meticulous planning by the Bangalore chapter of the Cancer Patients Aid Association (CPAA). No one could have thought of a more lively way to score a point against a life-threatening disease. And to assert that a little music and a lot of goodwill is all it takes to reaffirm a cancer patient's faith in life.

The Economic Times
8th January 1999

Profile

Meet Manju Gupta Director Rehabilitation since 1988, who has been a newsreader on Mumbai Doordarshan, did a course in Mass Communication in USA and then joined Sloane Kettering in the PR department and worked there for 10 years.

On her return to India she made an audio visual film for CPAA which gave a big boost to us since people could see the work in which we were involved. Manju then decided to help run the Rehabilitation Centre for cancer patients. When she took charge she decided that the centre would not be another run of the mill affair but a one – stop restoration therepy. People should not buy the products out of pity for the patients but also because-we give quality at competitive rates.

Since then the terracotta and designer stationery items made at the centre are much coveted and people wait for the Society exhibition in which the CPAA stall is a complete sell-out.

The tailoring department has an order to supply linen to the Taj Group of Hotels all over India.

Manju takes part in TV shows, looks after all the needs of the patients who come to CPAA and makes sure that they are all encouraged to become self-sufficient "The human being and his dignity is our primary concern" she says.

Giving Hope for Saving Lives

CANCER PATIENT'S AID ASSOCIATION

At Mumbai

Gulshan Hodiwala
King George V. Memorial
Dr E. Moses Road, Mahalaxhmi,
Mumbai - 400 001
Tel: (022) 4924000 / 4928775
Fax: (022) 4973599

Siloo Jasdanwala
5, Malhotra House, Opp. GPO
Mumbai - 400 001
Tel: 022 - 269 8964 / 269 3790
Fax: 022 - 269 7255

At Delhi

Madhu Hukku
C-1 / 807 Mayfair Towers
Charmwood Village, Near Suraj
Kund Dist. Faridabad, Hariyana,
Tel: 0129 - 252881

Manju Dar
AB870, Sarojini Nagar
New Delhi - 110 023

At Bangalore

Sarla Kolhi
1330, 13th Cross, Indiranagar
2nd Stage, Bangalore - 560 038
Tel: 080 - 525 1005

At Pune

Dolly Rizvi
5, Angel Appts. 9, Kalyani Nagar
Yerwada , Pune - 411 014
Tel: 020 - 682224 / 680066.

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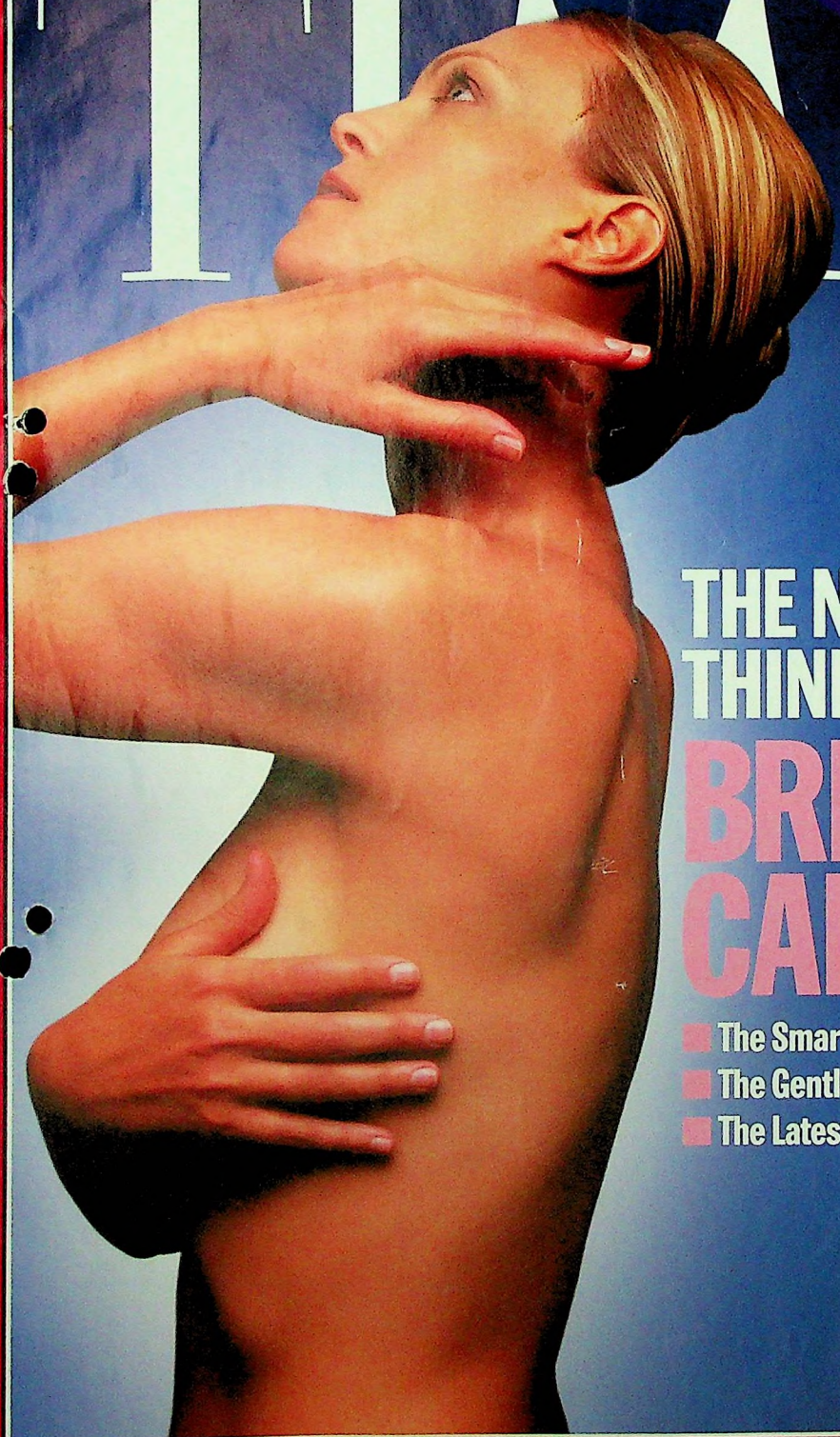
TIME

global BUSINESS
DoCoMo Woes



THE NEW THINKING ON BREAST CANCER

- The Smartest Drugs
- The Gentlest Treatments
- The Latest on Mammograms

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LLOYD FRANCIS—SIPA

TARMAC INSECURITY: Armed troops move into the area, but only after the attack

Murder in the Airport

After one of his top officials is killed, Afghanistan's leader struggles to keep his fragile nation united

By TIM MCGIRK KABUL

STANDING IN THE COLD RAIN ON A rocky hillside cemetery outside Kabul, Afghan leader Hamid Karzai watched grimly as the body of his assassinated minister, Abdul Rahman, was lowered into the ground. "We will capture his killers," Karzai vowed, "and we will punish them."

Grabbing the culprits may be the easy part. Punishing them is a different matter. The suspects include senior military and intelligence officials in Karzai's fragile coalition government who belong to the Northern Alliance, an Afghan faction that didn't want Karzai in the first place. By going after the killers, the country's interim leader is headed for a showdown with the powerful warlords who control Afghanistan's foreign affairs, military and security forces—and even his own palace guards. His green-striped cape sodden with rain during the funeral ceremony, Karzai never looked so alone.

The death of Rahman, the tourism and aviation minister, is a tragically classic Afghan murder drama. And it raises fears that Karzai's coalition, welded in part by foreign aid and B-52 bombers, might be falling apart. Karzai's aides claim the minister's killers tried to mask the assassination by making it seem spontaneous. It occurred last Thursday at Kabul's airport, where for two days, 800 pilgrims on their way to the hajj had been stranded, hungry, thirsty and freezing in their white cotton robes and sandals. Their plight was largely a result of Rahman's incompetence: his staff had failed to fill out the necessary paperwork for two Saudi jumbo jets to land at Kabul and whisk the pilgrims off to Mecca.

Rahman, meanwhile, had gassed up an Antonov turboprop belonging to Ariana, the national carrier, for a private jaunt to India with friends. When the shivering pilgrims saw Rahman and his fur-clad pals climb aboard, it was easy for the assassins, mingling with the hajis, to roust the crowd into action. Several people charged the runway and threw themselves in front of the turboprop's wheels. The pilot stopped, and Rahman made the mistake that cost him his life: he opened the hatch to shoo away the pilgrims.

Then the assassins stormed the plane. Whipping out knives, they stabbed and beat Rahman to death. Neither the police nor international security forces, which patrol a different part of the airport, intervened. Later that night, when the Saudi charter jets showed up to transport the pilgrims, several of the suspected killers flew with them. Karzai has asked the Saudis to hand over General Abdullah Jan Tawhidi, a military intelligence chief, and General Kalandar Beg, a deputy defense minister, along with other suspects. The Saudis have agreed to help. In all, says a Karzai aide, more than 20 Afghan officials were involved in Rahman's murder.

As he presides over a nation still seeking a semblance of normality, Karzai is struggling to contain the damage. He claims that the motives for Rahman's death were "personal, not political." But Rahman, like Karzai, was a royalist, and some diplomats believe the killing was the Northern Alliance's way of demonstrating opposition to the planned return to Afghanistan this spring of Mohammed Zahir Shah, 87, the exiled monarch. An Afghan patriarch was heard muttering at the funeral: "This killing is a clear warning to Zahir Shah's people."

Across town was another sign of distress. At Kabul Stadium—the scene of ghastly Taliban executions in the past—Afghans squared off against international peacekeepers in a football game, the first live entertainment in the capital in nearly a decade. The event was marred by stone throwing, tear-gas firing and beatings as foreign troops struggled to hold back thousands trying to cram into the already brimming 30,000-seat stadium. Against the warlords, Karzai is similarly outmanned. Though he can count on widespread support from both the West and Afghans sick of the fighting and bullying, his rivals have weapons and the inclination to use them. Murder is a time-honored tool of Afghan politics, but this is one crime that Karzai cannot afford to let go unpunished—or he could be its next victim. ◻

BULLITT MARQUEZ—AP

JEWEL SAMAD—AFP

SHAKY ALLIANCE: The assassination of Rahman, top, puts further strain on the brittle coalition led by Karzai, below

Rethinking BREAST CANCER

New detection techniques and treatments are exciting—and confusing. A guide to saving lives

By CHRISTINE GORMAN

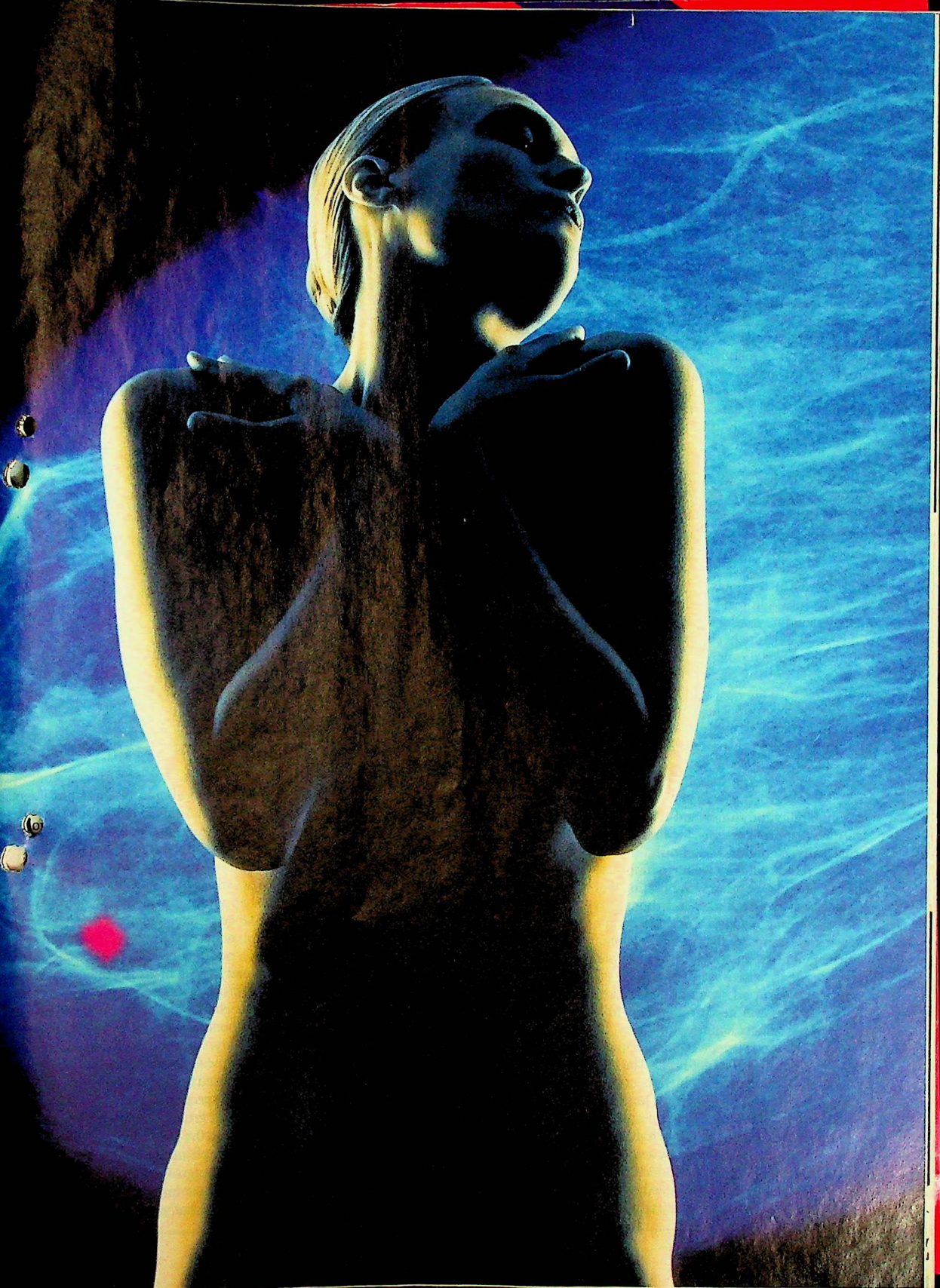
NANCY ULENE, 43, WASN'T particularly worried when a routine mammogram turned up something her radiologist thought was fishy. She had had a tumor seven years earlier that turned out to be benign. But this time was different. A biopsy confirmed that Ulene, the niece of former *Today* show medical expert Art Ulene, had ductal carcinoma in situ, or DCIS, a growth that is variously described as either an early-stage breast cancer or a precancerous lesion. "It was very confusing," says Ulene, a color stylist for Walt Disney TV Animation. "I needed to know more."

What she soon learned was that the kind of cancer she had—a group of malignancies so tiny that they were rarely seen before the advent of mammograms powerful enough to spot them—is at the heart of a raging debate in the cancer community. Doctors know what to do when they find tumors the size of marbles or plums. That's what surgery, radiation and chemotherapy are for. But what do you do with cancers the size of pencil points? Do you treat them as you would a massive tumor? Do you leave them alone? Should you even be looking for them in the first place?

This year, according to the American Cancer Society, some 200,000 women (and 1,500 men) will learn that they have breast cancer—up from a little more than 100,000 two decades ago. While the death rate from the disease has dropped modestly over the past decade, there is a growing sense of frustration among cancer experts. Part of the problem is DCIS. Thirty years ago, these miniature tumors, which usually don't spread into the rest of the body, were diagnosed in some 6% of breast-cancer patients. Today the ratio is closer to 20%, largely because of advances in detection techniques. Yet the treatment of choice is still surgery followed by radiation. "We may be far overtreating our pa-

Photo-Illustration for TIME by Howard Schatz

MAMMOGRAM PHOTO: PHOTO RESEARCHERS



tients," says Dr. Julie Gralow, an oncologist at the Fred Hutchinson Cancer Research Center in Seattle. "We've now got women being diagnosed with tumors that probably never would have been treated if we didn't have mammography. They probably would have lived long, natural, healthy lives never knowing they had breast cancer."

The long-simmering debate over the value of routine mammograms flared up again last month because of new questions about whether the test has been sufficiently proved to save lives (*see box*). But the mammography squabble masks a deeper problem: advances in screening and diagnostic technology have outpaced treatments, leaving cancer patients and their doctors struggling to make treatment choices neither are prepared to make.

That's the bad news. The good news is that the situation is on the mend. Basic research into the molecular chemistry of cancer is well funded and advancing steadily, delivering better diagnoses and smarter drugs. Meanwhile, a series of dramatic improvements in the tools of treatment are moving into clinical trials, promising patients kinder, gentler ways to treat their cancers. Among the highlights:

▶ Surgeons are developing several techniques that destroy tumors while sparing more breast tissue—without reducing the chances of survival. (This can be particularly important for small-breasted women who don't necessarily have a lot of tissue to spare in the first place.)

▶ Doctors are experimenting with new ways to deliver lethal radiation that more closely targets the tumor and takes just a few days at most—compared with the more usual six-week regimen—to finish the job.

▶ Researchers who are trying to minimize the need for chemotherapy are finding that patients can avoid chemo altogether if just one or two cancer cells are discovered in a lymph node—apparently these cells are not active enough to cause any further trouble.

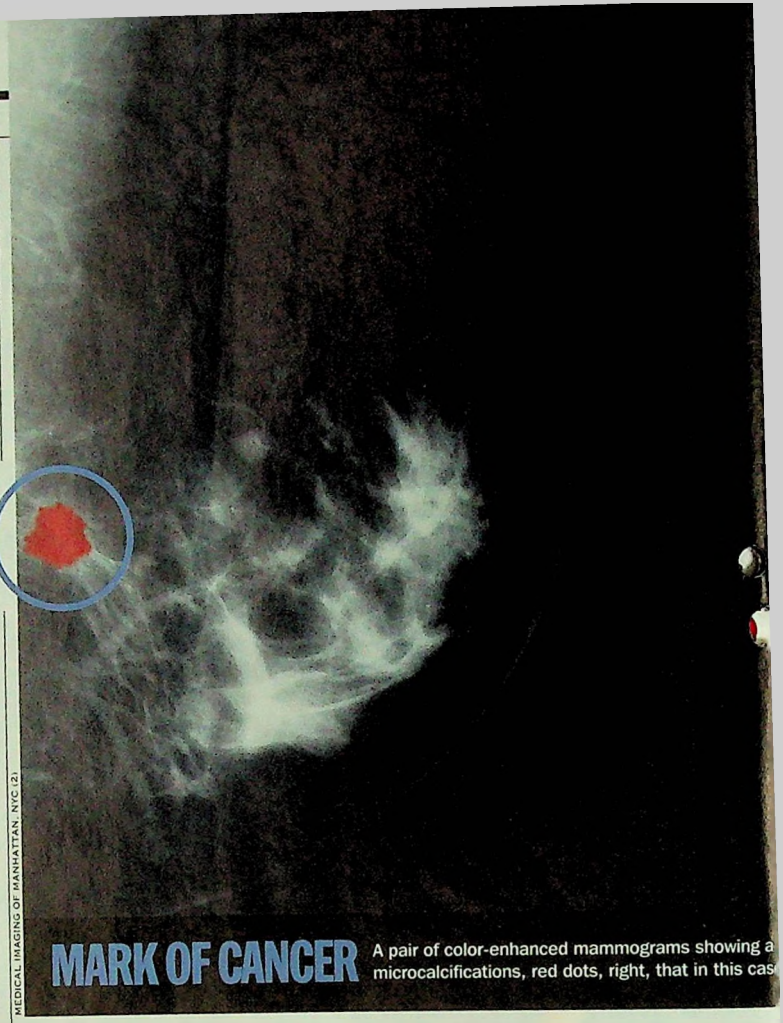
MOST OF THESE NEW APPROACHES still need to be more fully tested before they can be widely adopted. Some of them will undoubtedly fail. The ultimate prize, which could be available within the next 10 to 15 years, would be a diagnostic test that determines which genes in a particular tumor have gone awry. As doctors are increasingly aware, it's not just a tumor's size but its underlying biology that determines how quickly it will grow. Genetic tests may one day accurately identify those tumors that are likely to spread and those that are not. The tests may also tell doctors to which drugs your particular tumor is most vulnerable.

Before peering any further into the future, however, it helps to know a little biology. Most breast cancers begin in the milk ducts, narrow passageways that radiate throughout the breast. A few cells, for reasons that are not completely understood, start accumulating genetic mistakes that cause them to grow abnormally. Eventually the cells develop into DCIS. The good thing about DCIS cells is that they haven't spread beyond the milk duct. The bad thing is that they are malignant. "Some people call DCIS precancer, but it's not precancer," says Dr. Dennis Slamon, director of breast-cancer research at the UCLA School of Medicine. "It's preinvasive. It's cancer that hasn't invaded outside the breast ducts."

After a tumor starts to break out of its milk duct, it's often still quite small. About the smallest tumor a mammogram can pick up is 0.5 cm to 1 cm in diameter. By contrast, the average cancers that are felt either by women or their physicians are around 2.5 cm. Even though mammograms still miss about 10% of all tumors, it's their ability to spot smaller tumors, which are generally easier to treat, that keeps women coming back for their annual appointment.

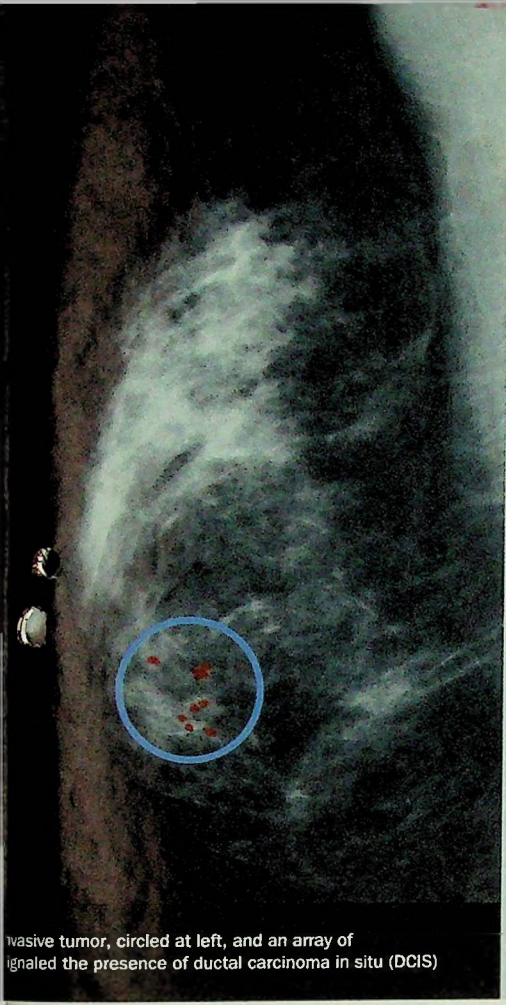
Once the cancer puts down roots in the lymph nodes, the prognosis gets worse. The lymph nodes act as a kind of sewer system for many types of toxins and wastes. Tumors growing in the lymph nodes have a greater chance of breaking off and traveling to the bones, brain, lungs or other parts of the body, where they can seed new growths, called metastases. Here again doctors used to think that any breast cancer that had spread to the lymph nodes must have been growing a long time. Now they realize that the fact the cancer has shown up in the lymph nodes may have more to do with how aggressive it was from the start than with how long it has been growing.

That's what makes DCIS treatment so



MEDICAL IMAGING OF MANHATTAN, NYC (2)

MARK OF CANCER A pair of color-enhanced mammograms showing a microcalcifications, red dots, right, that in this cas



ıvasive tumor, circled at left, and an array of
ignaled the presence of ductal carcinoma in situ (DCIS)

MAMMOGRAPHY

What All the Fuss Is About

Do routine mammograms actually save lives? For the past two years, academics have been furiously arguing the question. Two Danish scientists are convinced that they don't. A host of medical and advocacy groups in the U.S. is just as certain that they do.

Wasn't this issue decided long ago? You would have thought so. Since the 1960s, mammograms have been tested with seven different randomly controlled clinical trials. Most of these trials concluded that early detection via routine mammograms significantly reduces a woman's risk of dying from breast cancer—by as much as 30%. But some critics suspect that those results might have been unintentionally skewed by scientists seeing only the results they hoped to see. The two Danish researchers judged these old studies by today's standards of what constitutes a good clinical trial and concluded that five of the studies were so shoddy or primitive that their conclusions could not be trusted. The data from the remaining two studies, taken together, showed no lifesaving benefit from routine mammography.

How is that possible? Mammograms are not perfect. Even the best miss 10% of breast cancers. Unlike pap smears, which detect precancerous lesions that can easily be removed, mammograms find growths that are already malignant and that are more difficult to remove. Whether or not the cancer grows another year or two before it becomes a lump that can be felt may ultimately not make much of a difference to long-term survival.

Do mammograms have any other drawbacks? Sure. They are associated with a high rate of false positives—readings that come back abnormal even when no cancer is present. The result is a lot of anxious women getting called back for another mammogram or told they have to undergo a biopsy.

Will we ever know the truth about mammograms? There's a push to make public the raw data from some of the original studies. Without new studies, that's probably the closest we are likely to come in the near future to a scientific answer.

Should I cancel my next appointment? Absolutely not! Mammograms find more tumors at earlier stages of development than any other screening test currently available. That gives women options they might not otherwise have—forgoing chemotherapy, for example, or opting for breast-sparing surgery and hormonal therapy. And, who knows, they might just save your life. —C.G.

controversial. What if most of the tiny tumors that show up in high-resolution mammograms are the ones that grow the slowest or maybe even disappear of their own accord? It probably doesn't matter too much how quickly you treat these slow-growing tumors; most women would survive. And if that's the case, wouldn't it make sense to leave those tumors alone until you could figure out whether they are going to grow? Some breast-cancer experts even speculate that more women may die with these tumors *in* their breast than because *of* them.

An intriguing study on invasive tumors, begun in 1988, provides some clues. The trial included about 1,200 women whose tumors were less than 2 cm across with no evidence of malignancy in their lymph nodes and whose cancer cells looked, under the microscope, as if they weren't particularly dangerous. Although these women did not receive the "watchful waiting" approach pioneered in prostate-cancer patients, they weren't treated as aggressively as they might have been. For five years after their tumors were surgically removed, doctors did nothing more unless there was a recurrence. Though 11% of the women did in fact develop a second cancer, their survival rate (and this is the key) was comparable to that of another group of women who had undergone chemotherapy (with or without the drug tamoxifen) at the time of their surgery.

NO ONE IS RECOMMENDING A wholesale "cut and wait" approach for breast cancer—particularly on the basis of a single study. For one thing, waiting to see how aggressive a cancer truly is makes a lot more sense for men in their 80s than for women in their 40s.

The question about what to do with DCIS is also rife with extenuating factors. If DCIS never left the breast ducts, physicians could safely ignore it. No one knows for sure, but at least one study suggests that perhaps 40% of DCIS lesions will develop into invasive tumors that, if left untreated, could eventually prove fatal. That means that maybe 60% of DCIS cases never threaten a woman's health—and therefore these growths do not need to be removed.

Before the routine use of mammograms, most cases of DCIS were discovered accidentally, often during other surgeries. Thanks to better screening, the absolute number of DCIS cases has jumped sevenfold in the U.S. over the past three decades. "At the moment, we don't know which women diagnosed with DCIS might be able to get by with minimal treatment," says Dr. Eric Winer, director of breast oncology at the Dana-Farber Cancer Institute in Boston. As a result, most doctors agree that it's prudent to treat all DCIS cases as if they are dangerous. (In the past couple of years, however, some surgeons have started treating the tiniest, least aggressive DCIS lesions by excision alone, forgoing radiation, provided they can get wide, cancer-free margins around the tumor.)

That's not the only dilemma with DCIS. Radiologists don't actually see a DCIS lesion—they see its footprint in the calcified

Anatomy of a Tumor

Every breast cancer is a little different, but many follow a fairly standard course. How each is treated depends on how early it is discovered, how aggressively it is spreading and how it responds to antihormone treatments and other drugs

PRECANCEROUS

Normal
The cells lining the duct are orderly and well differentiated

Hyperplasia
A few extra cells accumulate

Atypical ductal hyperplasia
The cells start looking more and more abnormal

STAGE 0

DCIS with Micro-calcifications

■ THE DEFINITION

Cells that look like cancer but have not invaded surrounding tissue are called ductal carcinoma in situ (cancer confined to the duct). The lesions may be tiny as pinpoints and may pop up throughout the breast

■ THE OPTIONS

Patients whose lesions are tightly focused can be treated with lumpectomy and radiation. Some surgeons think surgery alone may be sufficient in certain cases

■ THE OUTLOOK

Very good. Virtually no one dies of breast cancer within five years of treatment for DCIS. No one knows what percentage of DCIS lesions eventually become invasive

STAGE I

Invasive Ductal Ca

■ THE DEFINITION

Some of the cells from the tumor, which now measures 2 cm or less, spill out of the duct. There is no evidence of cancer in the lymph nodes

■ THE OPTIONS

Mastectomy or lumpectomy plus radiation. Lymph nodes are biopsied. Chemotherapy or tamoxifen may be recommended for some women

■ THE OUTLOOK

Anywhere from 95% to 98% of women are doing fine five years after treatment. Most will live much longer

STAGE III

■ THE DEFINITION

The cancer has really taken hold in the lymph nodes. Even a tumor less than 1 cm in size is considered Stage III if several lymph nodes are involved

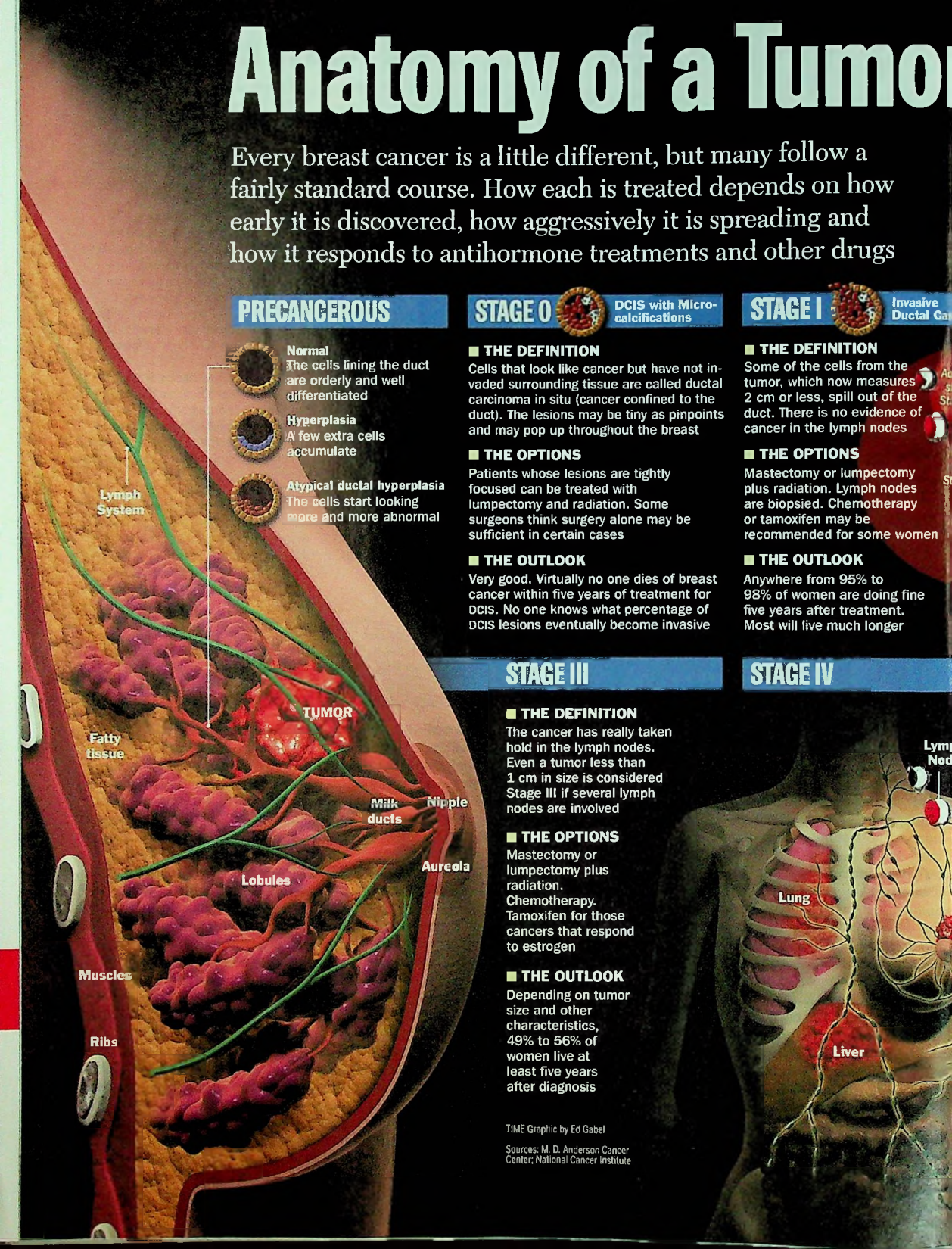
■ THE OPTIONS

Mastectomy or lumpectomy plus radiation. Chemotherapy. Tamoxifen for those cancers that respond to estrogen

■ THE OUTLOOK

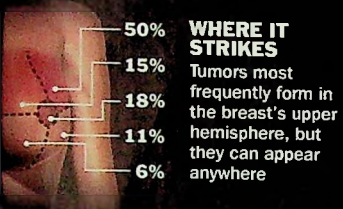
Depending on tumor size and other characteristics, 49% to 56% of women live at least five years after diagnosis

STAGE IV



TIME Graphic by Ed Gabel

Sources: M. D. Anderson Cancer Center; National Cancer Institute



WHERE IT STRIKES
Tumors most frequently form in the breast's upper hemisphere, but they can appear anywhere

STAGE II

■ THE DEFINITION
Most tumors in this category measure 2-5 cm but have not spread to the lymph nodes

■ THE OPTIONS
Mastectomy or lumpectomy plus radiation. Chemotherapy is used for any cancers that have spread to the lymph nodes and may even be indicated for larger node-negative tumors. Tamoxifen is prescribed for those cancers that respond to estrogen

■ THE OUTLOOK
Depending on tumor size and other characteristics, 76% to 88% of women live at least five years after their diagnosis

STAGE IV

■ THE DEFINITION
The cancer has spread beyond the breast, leading to secondary tumors in the liver, lungs, brain or elsewhere

■ THE OPTIONS
Most treatments are aimed at relieving symptoms or prolonging life a few months or years. Surgery or radiation to remove or at least try to shrink any tumors. Chemotherapy. Herceptin for those cancers that express an excess of the Her2 receptor. Tamoxifen or an aromatase inhibitor, if they haven't already been used, for those tumors that respond to estrogen. (Clinical trials of both herceptin and aromatase inhibitors in earlier stages of breast cancer are under way)

■ THE OUTLOOK
Studies indicate an average survival time of 18 months to 24 months. From 15% to 20% live at least five years after diagnosis

remains of dead and dying cells. What makes mammography as much an art as a science is that these so-called microcalcifications are often just a normal part of breast anatomy. It's the pattern of microcalcifications—whether new ones appear suddenly or line up in particular formations like soldiers in a row—that suggests something more sinister.

For a variety of reasons, radiologists in the U.S. tend to err on the side of caution. That is, they identify lots of "abnormalities," of which only 2% to 11% prove to be cancerous—either DCIS or an invasive tumor. Sometimes a second mammogram or an ultrasound provides the necessary reassurance. Other times, a biopsy—which entails the removal of some breast tissue—is required to resolve any ambiguity. Here the odds of finding cancer rise to about 25%, which means that 75% of biopsies come back negative.

For years many women got an ugly scar along with their answer because most biopsies began with a wide surgical incision. Nowadays, more breast centers offer such minimally invasive biopsies as the Mammotome, which relies on careful positioning of the breast to remove the least amount of tissue. "We're trying to reserve surgery for treatment, not diagnosis," says Dr. Joshua Gross, chief of breast imaging at Beth Israel Medical Center in New York City. "So many women I see have scars all over their breasts. The scars aren't from being treated. They're from doctors finding out if a woman even needs to be treated."

Thirty years ago, surgery meant mastectomy—removal of the entire breast. By the 1980s, studies had shown that for tumors that had not spread, only the portion immediately surrounding the cancerous growth needed to be cut away—provided the operation was followed by radiation therapy to destroy any wayward cancer cells the surgeon may have missed. Today, as more women are being treated for ever smaller tumors, doctors are finding that even these so-called lumpectomies can be further refined.

The new minimalist approach begins with the first cut, which many surgeons now place near the nipple, under the arm or in the lower portion of the breast so that any scars are much less obvious. Because many small tumors are confined to the duct or its immediate vicinity, doctors have learned they don't need to remove so much of the overlying fatty tissue as they used to. "Taking out too much fat was what led to the concavities and deformities we saw in the past," says Dr. Alexander Swistel, director of the Weill Cornell Breast Center in New York City. The remaining tissue can then be rearranged to fill in the void.

Doctors have also developed a new technique for determining whether a cancer has spread to the lymph nodes. Instead of taking 15 to 20 lymph nodes from in and around the armpit for further examination—a procedure that can lead to problems with swelling and disability of the arm—they are focusing on certain key spots called sentinel nodes. The surgical team injects a blue dye into the tissue from which it has just removed a tumor and traces its path through the lymph system. The first node or two that the dye reaches are presumably also the first nodes in which any cancer cells would take up residence. The sentinel nodes are removed and closely examined. If they are free of cancer, chances are all the other nodes are clear. Preliminary evidence suggests that this is indeed the case, though two randomized controlled trials of the technique are under way to make sure.

EVENTUALLY, WOMEN MAY BE ABLE TO forgo surgery entirely. Doctors at the M.D. Anderson Cancer Center at the University of Texas in Houston and the Weill Cornell Center in New York City are experimenting with high-frequency radio waves that can literally cook tumors from the inside. Using ultrasound to guide them, doctors insert a multipronged probe into a tumor. The prongs open up like the spokes of an umbrella and melt malignant cells without burning surrounding breast tissue. So far, the procedure has been performed only on women who were planning to get a mastectomy or lumpectomy anyway. But early results have been encouraging enough that physicians hope to test it as a stand-alone procedure this year.

One of the drawbacks to minimally invasive surgery, in the eyes of many women, is that it is usually followed by radiation. Currently, doctors shoot high-powered beams across the affected breast five days a week for six or seven weeks. But it has become increasingly clear, particularly with smaller tumors, that if the cancer recurs, it usually does so in the original spot from which the tumor had been removed. By focusing radiation more precisely on the place where the original tumor occurred, says Dr. Silvia Formenti, chairwoman of radiation oncology at New York University School of Medicine, "we think we can make radiation better and easier for the patient."

Taking a page from treatment manuals

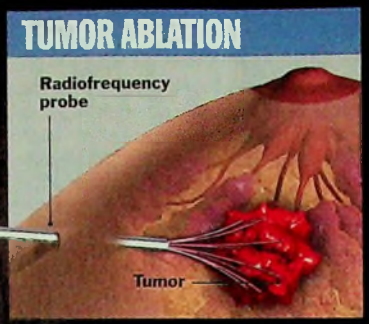
THE CUTTING EDGE OF CANCER TREATMENT

Surgery, radiation and chemotherapy are still the first line of defense against breast cancer. But exciting new techniques are entering clinical trials and, if they work, may eventually replace the old standards with kinder, gentler treatments

TIME Graphic by Ed Gabel

Sources: Acoustic Pharma Therapeutics, M. D. Anderson Cancer Center, Resetta Inplasmatics

TUMOR ABLATION



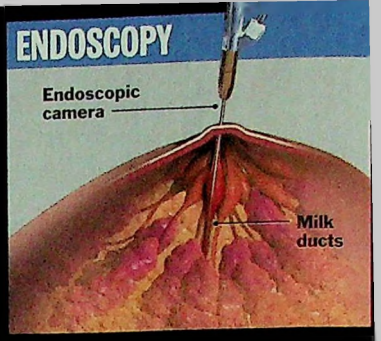
HOW IT'S DONE

Cancers can be frozen or vaporized with lasers or high-energy radiowaves delivered by a probe through a tiny incision. In one technique, the probe opens like an umbrella inside the breast

AVAILABILITY

Already used for liver tumors. Clinical trials for breast cancer are under way, but could take five years to complete

ENDOSCOPY



HOW IT'S DONE

Tumors can be examined with a miniature fiber-optic camera that is inserted through the nipple and into a milk duct. Eventually surgeons may be able to treat tumors through the same tiny probe

AVAILABILITY

The fiber-optic scope was okayed by the FDA last summer. Using it for treatment may be less than five years away

for prostate cancer, a few doctors have implanted tiny radioactive "seeds" in the breast to ensure that the maximum amount of radiation is delivered near the tumor site. They leave a small, balloon-tipped catheter in the breast after a lumpectomy. The balloon is filled from the outside with the radioactive material for five to 10 minutes twice a day. After five days, both catheter and contents are removed.

Don't have five days to spare? Doctors in the U.S. and Europe think they may be able to deliver all the radiation that's needed while a woman is still on the operating table. In an experiment conducted on 15 women in England, physicians inserted a tiny coil into the cavity created by the removal of a tumor. The bottom of the coil was shielded in lead to protect the heart and lungs, while the breast tissue was stretched around the coil. As the surgical team left the room to avoid exposure, the device delivered a full course of radiation treatment at once. After 25 minutes, the coil was removed. In 18 months of follow-up, none of the breast cancers have recurred.

Unfortunately, some cancers do reappear, sometimes far from their original site. This is where chemotherapy can make a difference. Once again, it's not always clear who will benefit most. A concrete example helps explain:

Many doctors would recommend chemotherapy to a woman whose tumor measures 2 cm across, even if it has shown no sign of spreading to the lymph nodes. Why? There is always the possibility that some cancer cells have already escaped to the rest of the body through the bloodstream.

How often does that happen? Statisticians estimate that 20 of every 100 women who get only mastectomy (or lumpectomy plus radiation) for a 2-cm tumor that has not spread to the lymph nodes would, all other things being equal, suffer a recurrence sometime in the next five to 10 years. Fourteen of those tumors would have come back regardless of whether any additional therapies had been tried. The remaining six would have been prevented by chemotherapy. "For a 6% improvement, that's a lot of women who have to accept chemotherapy," says Dr. Gralow at the Fred Hutchinson Cancer Research Center in Seattle. But there is no way to figure out in advance which six tumors actually needed to be treated.

That may change as scientists learn more about the genetic alterations that transform a normal cell into a malignant one. Last month a group of scientists fr the U.S. and the Netherlands published a

PREVENTION

Estrogen: A Villain and a Possible Savior

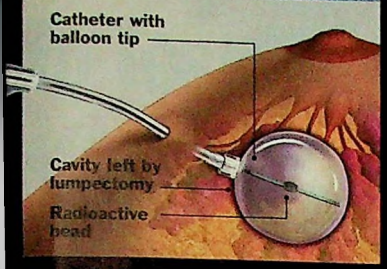
There is no single cause for breast cancer, but one major factor is estrogen. That's a shocking thought. The same hormone that softens our skin, thickens our hair and fills out our hips and breasts also feeds disfiguring tumors. Rates of breast cancer are highest in developed nations, in part, scientists believe, because with better nutrition we reach menses earlier and menopause later, allowing estrogen to course through our bodies for that much longer.

If there is a bright side to all this, it is that estrogen is now pointing the way to new breast-cancer treatments. One of the most exciting developments in the field is a new class of drugs called aromatase inhibitors, which for postmenopausal women are already in use against late-stage tumors and may prove even more effective when tumors are caught early. Aromatase inhibitors block the action of an enzyme that these women need to produce estrogen. Two new studies suggest that the drugs can shrink tumors before surgery and also perhaps prevent breast cancer from recurring. More than 20,000 women are enrolled in clinical trials designed to show just how effective the aromatase inhibitors are in early cancer and how best to use them.

These drugs could one day replace tamoxifen, which is routinely given to women at high risk for recurring tumors, and raloxifene, a newer drug that was originally designed to prevent osteoporosis but also appears to block breast cancer. Known as "designer estrogens," tamoxifen and raloxifene work by taking the plac of the body's natural estrogen on the surface of breast-cancer cells preventing the real thing from stimulating tumor growth.

Five years ago, doctors and their patients hailed tamoxifen, which was the first drug approvec for reducing the risk of getting breast cancer (rather than just treating it). But tamoxifen is far from perfect. It increases the risk uterine cancer and potentially fal blood clots. Raloxifene appears t provoke fewer side effects, but th results from a head-to-head stuc

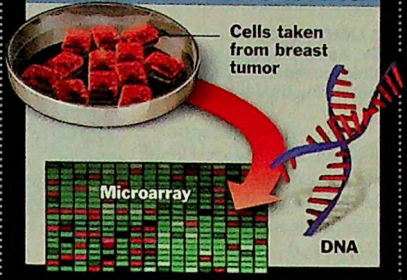
TARGETED RADIATION



■ HOW IT'S DONE
After a lumpectomy, a tiny radioactive bead is delivered directly into the tumor site through a small balloon-tipped catheter. Treatment takes a matter of days, not weeks

■ AVAILABILITY
Clinical trials on 70 patients nationwide have been completed. The procedure is awaiting FDA approval

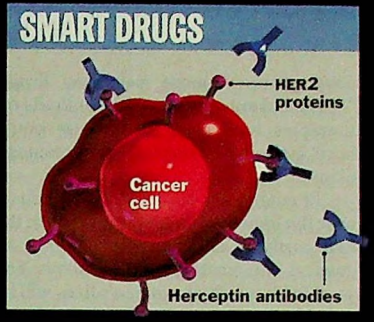
MOLECULAR FORECASTING



■ HOW IT'S DONE
With microarrays, scientists can study patterns of gene activity using strands of cancer DNA and predict which tumors are likely to spread. The technique may someday be used to design customized treatments

■ AVAILABILITY
Clinical trials for breast cancer are starting this year; treatment may be widely available within the decade

SMART DRUGS



■ HOW IT'S DONE
As scientists come to understand at the molecular level precisely how tumors form, they are designing a new generation of smart drugs that bind to specific receptors or block particular proteins

■ AVAILABILITY
Herceptin, the first of these smart drugs for breast cancer, is available for certain advanced cancers

paper in the research journal *Nature* describing a molecular test they have developed that may predict, at the time of surgery, which cancers will be likely to metastasize—and therefore might benefit from chemotherapy. Using so-called DNA microarrays, the researchers analyzed some 25,000 genes from the breast cancers of 100 women. By winnowing the number of relevant markers to about 70 genes, they produced a DNA profile that correlated closely with the women's actual outcomes. "There's not much that stands in the way of this test being used clinically," says Stephen Friend, one of the paper's authors and a co-founder of the biotech firm Rosetta Inpharmatics. Clinical trials could begin, he believes, within the year.

Such a test might prove particularly helpful in determining what to do about the so-called micrometastases that pathologists are starting to discover in some women's lymph nodes. Once again, better detection techniques have revealed minute clumps of cancer—0.2 mm across—that are smaller than anyone had ever seen before.

UNTIL RECENTLY, THE PRESENCE OF any cancer in a lymph node would be a clear signal that chemotherapy was required. But at the upcoming meeting of the American Society of Clinical Oncology in May, a group of cancer experts will recommend that these minute malignancies be left alone, as long as the original breast tumor is small. "We used to seek out and destroy every cell," says Dr. Eva Singletary, a breast surgeon at the M.D. Anderson Center in Houston, who chairs the expert panel. "Now we try to target and control our treatment."

Ideally, Singletary would like to be able to tailor each woman's treatment to the characteristics of her particular tumor. Already scientists have identified a biological marker called the HER2 receptor, whose presence usually signifies a very aggressive cancer. For the past four years, a drug called Herceptin has been given to women with metastatic tumors that make a lot of the HER2 protein. Now trials are being conducted to see if Herceptin, which may have some deleterious effects on the heart, will nonetheless help other women with smaller tumors that haven't yet spread.

Herceptin is only a beginning, says UCLA's Slamon, who identified the HER2 receptor. There are bound to be other cancer proteins that pharmaceutical manufacturers can use as targets as they

paring the two drugs won't be lable until 2009.
Meanwhile, researchers are ng better at predicting who is t likely to benefit from which gner estrogen. Raloxifene, it s out, is most effective for the menopausal women who have rally high levels of estrogen. r tests suggest that tamoxifen s little or no benefit to women carry the BRCA1 mutation, one o genetic mutations known to e an inherited form of breast er, but it can help lower the f breast cancer in women ing a variation of the gene d BRCA2. For now, women who are taking tamoxifen should continue doing so. But in the future, doctors will almost certainly have more drugs to choose from. They may, for example, use designer estrogens and aromatase inhibitors in sequence to try to keep breast cancer cells off-balance.

The ultimate goal, of course, is to keep breast cancer from taking hold in the first place, and estrogen will play a role in achieving that. One idea that researchers have begun to test is temporarily suppressing the body's natural estrogen and thus providing birth control along with protection from breast cancer. This could be accomplished by combining an ovulation-stopping drug with tiny doses of female hormones to protect tissues like bone and brain. A pilot study conducted at the University of Southern California in women with a family history of breast cancer showed that such a dosage regimen reduced breast density, making mammograms easier to read. An added benefit: the treatment cut their menstrual cycles to three a year. —*By Shannon Brownlee.*
Reported by Sora Song/New York

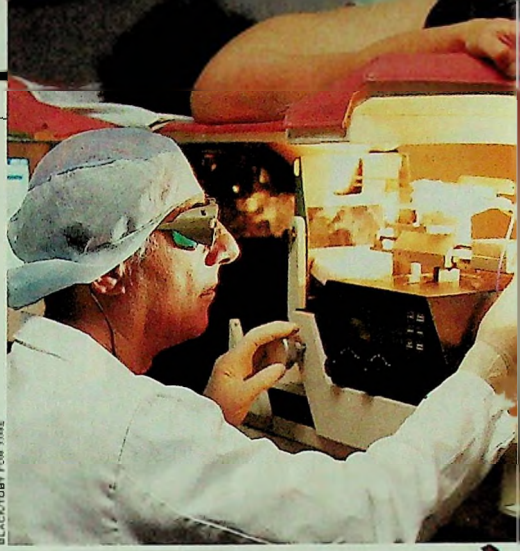
TAMOXIFEN: Prevents natural hormones from feeding tumors


JAMES KING-HOLMES/SPL—PHOTO RESEARCHERS

develop new, more selective drugs. "Using a combination of [these kinds of] therapies earlier in the disease could have a dramatic impact on outcomes," Slamon says.

It might also lay to rest any debate over the benefits of mammography; in the final analysis, early detection is only as good as the treatments that follow. You want to know which women's lives will be saved by surgery, radiation, chemotherapy or hormone treatment. Otherwise, you risk doing more harm than good.

That's why it helps, when trying to sort through the current unsettled state of affairs in breast cancer, to take the long view. "There's always a trend or an issue that everyone's chasing after," says Fran Visco, president of the National Breast Cancer Coalition. "I do think we're at a place where we can begin asking some of those questions regarding targeted therapy. But I don't think we're going to get the answers next month or next year."



BLACK STAR FOR TIME

A LIGHTER TOUCH: Dr. Kambiz Dowlat of Chicago readies a laser for vaporizing breast tumors

In the meantime, women like Nancy Ulene who discover they have breast cancer have to decide what to do with their lives and their breasts based on information currently available. There are days when many women would probably agree with Ulene's assessment that it's all a "crapshoot" anyway. After much soul-searching, she finally opted for a partial mastectomy and tamoxifen. It may not happen today. It may not happen tomorrow. But eventually those decisions will start to get easier. ***—Reported by Janice M. Horowitz, Alice Park and Sora Song/New York and Jeanne McDowell/Los Angeles***

FOR MORE INFORMATION

The National Cancer Institute's hot line at **1-800-4-CANCER** can answer questions about cancer diagnosis and treatment and offer tips for preventing breast cancer. On the Web, visit **www.cancer.gov**

FIRST PERSON

Who Needs Breasts, Anyway?

By **MOLLY IVINS**

Having breast cancer is massive amounts of no fun. First they mutilate you; then they poison you; then they burn you. I have been on blind dates better than that.

One of the first things you notice is that people treat you differently when they know you have it. The hushed tone in which they inquire, "How are you?" is unnerving. If I had answered honestly during 90% of the nine months I spent in treatment, I would have said, "If it weren't for being constipated, I'd be fine." In fact, even chemotherapy is not nearly as hard as it once was, although it still made all my hair fall out. My late friend Jocelyn Gray found the ultimate proof that there is no justice: "Not just my hair, but my eyebrows, my eyelashes—every hair on my body has fallen out, except for these goddam little mustaches at the corner of my mouth I have always hated."

Another thing you get as a cancer patient is a lot of football-coach patter. "You can beat this; you can win; you're strong; you're tough; get psyched." I suspect that cancer doesn't give a rat's ass whether you have a positive mental attitude. It just sits in there multiplying away, whether you are admirably stoic or weeping and wailing. The only reason to have a positive mental attitude is that it makes life

MATTHEW MAHON FOR TIME

better. It doesn't cure cancer.

My friend Judy Curtis demanded totally uncritical support from everyone around her. "I smoked and drank through the whole thing," she says. "And I hated the lady from the American Cancer Society." My role model.

The late Alice Trillin wrote some brilliant essays on being a cancer patient, and I found her theory of "the good student" especially helpful. When you are not doing well at cancer—barfing and getting bad blood tests and generally not sailing through the whole thing with grace and panache—you have a tendency to think, Help, I'm flunking cancer, as though it were your fault. Your doctor also tends to look at you as though he is disappointed. Especially if you start to die on him.

You don't get through this without friends. Use them. Call them, especially other women who have been through it. People like to help. They like to be able to do something for you. Let them. You will also get sick of talking about cancer. One way to hold down the solicitous calls is to give your friends a regular update by e-mail, if you have it. If you work, I recommend that you keep right on doing so (unless you hate your job). Most companies are quite good about giving you time off when you need it, and working keeps you from sitting around and worrying.

Losing a part of a breast or all of one or both has, obviously, serious psychological consequences. Your self-image, your sense of yourself as a woman, your sense of your sexual attractiveness are going to be rocked whether or not you have enough sense to realize that tits aren't that important. I am one of those people who are out of touch with their emotions. I tend to treat my emotions like unpleasant relatives—a long-distance call once or twice or year is more than enough. If I got in touch with them, they might come to stay. My friend Mercedes Pena made me get in touch with my emotions just before I had a breast cut off. Just as I suspected, they were awful. "How do you Latinas do this—all the time in touch with your emotions?" I asked her. "That's why we take siestas," she replied.

As a final indignity, I have just flunked breast reconstruction. Bad enough that I went through all that pain for the sake of vanity, but then I got a massive infection and had to have both implants taken out. I'm embarrassed about it, although my chief cancer mentor, Marlyn Schwartz (who went to the Palm for lunch after every chemo session), has forbidden this particular emotion. So now I'm just a happy, flat-chested woman. ■

Molly Ivins was found to have Stage III inflammatory breast cancer in 1999

To Test or Not to Test?

The mammogram wars are raging again. The facts aren't all in yet, but don't cancel your appointment

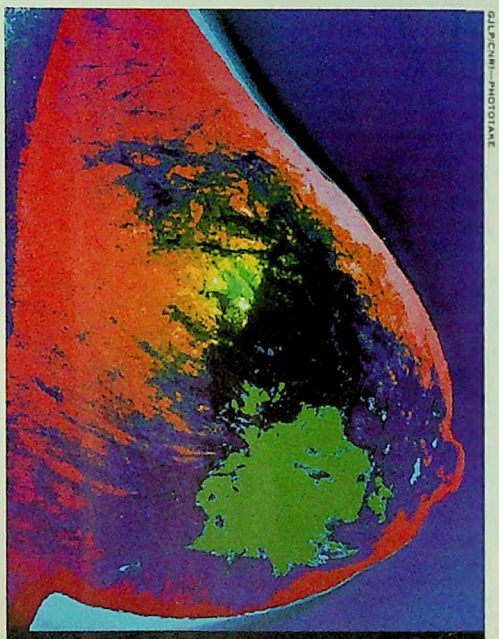
By CHRISTINE GORMAN

BREAST CANCER RESEARCHERS HAVE been arguing for two years about an issue that most women, in the U.S. at least, thought was settled: whether routine mammograms save lives. Given that tens of millions of these tests are performed each year, the women who get them deserve some clarity on the issue. Instead they're getting an old-fashioned academic feud with lots of heat and very little light.

The debate flared up again last week when an independent advisory panel to the U.S. National Cancer Institute concluded that a harsh critique by two Danish researchers of the data supporting mammography's benefits had enough merit that its conclusions should be addressed in the cancer database maintained by the NCI. For now, the cancer institute is not changing its basic recommendation that women age 40 and older undergo routine mammograms. But it is planning to review the policy. "This is a very complex issue," says Dr. Peter Greenwald, director of cancer prevention at the NCI. "It doesn't mean that it's wrong [to get a mammogram], just that it's less certain than we thought."

In trying to sort out what women should make of this controversy—and whether they need to keep their next mammogram appointment—it helps to have a little background. The most important thing to keep in mind is that the debate is about mammograms used to screen healthy women. Researchers are not talking about mammograms that are ordered after a lump has been discovered. Nor are they talking about women previously treated for breast cancer or those who are at high risk because of, for example, a strong family history of the disease.

The authors of the Danish study, which was published in the journal *Lancet* last October, focused on routine mammography of healthy women. They reviewed seven large clinical trials—several of them 30 years old—that were designed to figure out whether such mammograms actually saved lives. Using the most up-to-date standards of what makes a good clinical trial, they concluded that five of the studies were so primitive or of such poor quality that their conclusions could not be trusted. Those five included ones that found that routine mammograms reduce a woman's risk of dying from breast cancer by 30%. The two remaining studies found no benefit. The authors' conclusion: there is no reliable evidence that women who get mammograms live any longer than women who don't.



GILPCNRI—PHOTOTAKE

By focusing on whether women who get mammograms live longer than those who don't, scientists may have missed the point

The reaction in the medical community was immediate—and fierce. Critics argued that the methodology of the Danish review was flawed and that several studies were too hastily thrown out. Others pointed out that both mammography and breast cancer treatments are better now than they were in the 1970s and '80s, when some of those studies were conducted. Some breast cancer advocates have even wondered whether the Danish researchers might have had an economic or a political incentive to downplay the benefits of what are fairly expensive screening programs.

When you cut through all the arguments and counterarguments, what you realize is that everyone expects too much of mammograms. Even the best miss 10% to 15% of breast cancers. Mammograms are also associated with a high rate of false positives—particularly among younger women. In the U.S. only 2% to 11% of all "abnormalities" found in a routine screening actually turn out to be cancer. That translates into a lot of anxious women who are called back for another mammogram or advised to undergo either a needle aspiration or a biopsy. These can lead to problems such as scarring, infections and the complications of unnecessary surgery.

Despite these drawbacks, there are very real benefits to mammograms. The earlier a cancer is found, the more options a woman usually has with regard to treatment—something the Danish review did not address. Many women with smaller tumors, for example, may be able to forgo chemotherapy, opting for breast-sparing surgery and hormonal treatment. To these women, a few anxiety-provoking false positives may seem like a small price to pay.

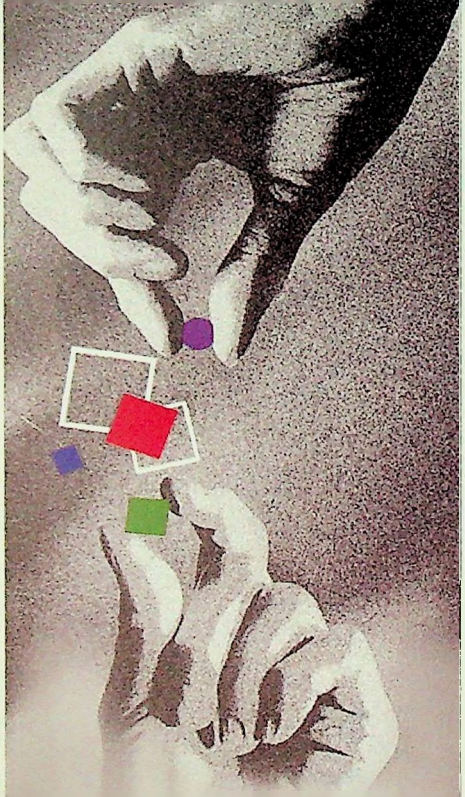
True, some slow-growing tumors will be treated when they probably don't need to be. And maybe someday doctors will know how to identify those cases and say with confidence, "We don't need to touch this cancer because it won't kill you until you're 85." But we're not there yet.

As with so many things in medicine, doctors and patients are left making decisions based on incomplete information. "We have to be honest about saying that [routine] mammography may not save your life," says Dr. Patricia Ganz, a professor at the schools of medicine and public health at the University of California at Los Angeles. But it can give a woman who discovers she has breast cancer options she might not otherwise have. And who wouldn't want that?

Three U.S. Stars. One Gold Medal. Get Ready for SPIN CITY

Not long ago, **Sarah Hughes** idolized Michelle Kwan. Now she and Sasha Cohen will challenge Kwan for Olympic glory

Photographs for TIME by Andrew Eccles



If it's earlier,

it's easier

Bangalore Institute of Oncology

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Raja Rammohan Roy Extension,
Off. Lal Bagh Double Road.
Bangalore-560027
Ph: 22225644, Fax: 22222146,
E-mail: bio@vsnl.com,
www.biohospital.org

*Note: Please be seated by not later than 4:30pm

PROGRAMME

Welcome Address

Dr. B.S. Ajaikumar - Chairman-BIO

Vision of BIO
Dr. Ganesh Nayak - VC & Managing Director

Introduction of : **Dr. Chidambaram**
by: **Dr. V.K. Iya** - Director - BIO

Inauguration and Address by

Dr. R. Chidambaram
Principal Scientific Advisor to the Govt., of India.
DAE - Homi Bhabha Chair Professor

Introduction of : **Dr. Dinshaw .K**
by: Dr. Nalini Rao - Director - BIO

Address by: **Dr. Dinshaw .K**
Director - TATA Memorial Hospital

Introduction of: **Sri. Sri. Sri. Jayendra Puri Mahaswamigal**
by: Dr. B.S. Ramesh - Director - BIO

Release of Souvenir & Blessings by:
Sri. Sri. Sri. Jayendra Puri Mahaswamigal

Honouring Ceremony
To recognise individual contributions to BIO

Introduction of:
Padma Vibhushan Justice M.N. Venkatachalaiah
by: Dr. K.S. Gopinath - Director - BIO

Presidential Address by:
Padma Vibhushan Justice M.N. Venkatachalaiah
Former Chief Justice of India

Vote of thanks
by: **Dr. B.S. Srinath** - Head of Surgery &
Former Managing Director - BIO

The Board of Directors,
Consultants and Staff of BIO
Cordially invite you for the inauguration of

THE LINAC CENTER.

By
Dr. R. Chidambaram
Principal Scientific Advisor to the Government of India
DAE - Homi Bhabha Chair professor

Chief Guest

Dr. Dinshaw. K
Director - Tata Memorial Hospital

Guest of Honour

Padma Vibhushan Justice M.N. Venkatachalaiah
Former Chief Justice of India

Presides

Paramapujya Paramacharya Jagadguru
Sri Sri Sri Shivaratnapuri Bhagavatpadacharya
Sri Sri Sri Thiruchi Mahaswamigal
Sends his blessing through
Sri Sri Sri Jayendrapuri Mahaswamigal
Deeksita Shishya of Paramapujya
Sri Sri Sri Thiruchi Mahaswamigal

Release of Souvenir

DATE: 10th JANUARY 2005 (Monday)
TIME: 4:30 p.m.
VENUE: Town Hall, Bangalore

On this occasion we also commemorate 15 years of dedicated public service in the field of Oncology

Bangalore Institute of Oncology

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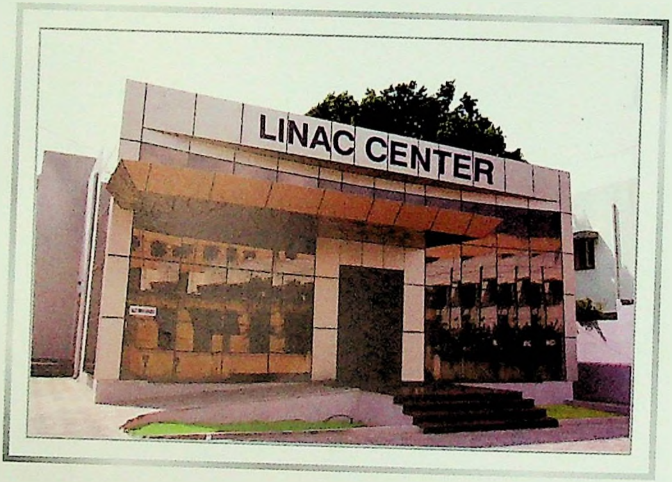
Bangalore-560027
Ph: 22225644, Fax: 22222146,
E-mail: bio@vsnl.com,
www.biohospital.org

*Note: Please be seated by not later than 4:30pm

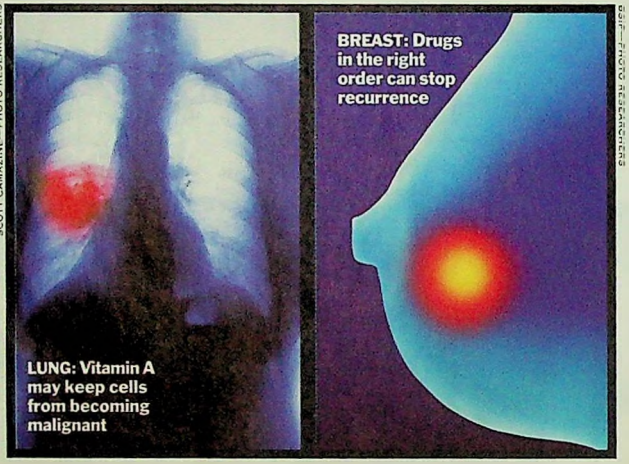
B/D Chairman – Dr Ajai Kumar, 107 beds, 230 staff
– Dr Suresh Nayak, MD
Mysore – Bharat Cancer Hospital
Shimoga – Dr Jayanath Dixit, Nalband Institute of Oncology & Research Centre
Curie centre – Radiotherapy,
CME, HE, & RV dental college
1997 – case against Central Govt re[illegible]



An Ounce of Prevention

Cancer doctors met last month to share the latest research on keeping tumors at bay. Here are the findings By Alice Park

AS CANCER SPECIALISTS from around the world gathered last month in Orlando, Florida, for the annual meeting of the American Society of Clinical Oncology, a new sense of optimism was in the air. It's not that cancer has been cured—there are too many different types of malignancies to hope for a universal treatment.



SCOTT CAMAZINE—PHOTO RESEARCHERS

GSIP—PHOTO RESEARCHERS

Rather, it's that doctors are beginning to piece together new strategies for keeping cancer from recurring and, in some cases, preventing it from taking root in the first place. As ASCO president Dr. Larry Norton puts it, "Cancer is not a bolt of lightning. It's more like a thunderstorm. We have plenty of time to close the windows if we know what to do."

One of those windows opens up right after a patient's initial treatment. It's becoming clear that whatever form that treatment takes—surgery, chemotherapy, radiation, medication—what doctors and patients do in the weeks afterward may determine whether a cancer comes back.

Breast cancer is a prime example. For more than two decades, women with early-stage, estrogen-sensitive breast cancers have been treated with surgery followed by a combination of tamoxifen and chemotherapy. Adding tamoxifen seemed to make sense, since it blocks estrogen's cancer-promoting effects. It turns out, however, that tamoxifen may act as a spoiler, preventing the chemotherapy agents from entering cancer cells and doing their job. In a paper presented at the conference, researchers reported on a finding that should change the way doctors treat patients from now on; after eight years of follow-up exams, women who waited until their chemotherapy was complete before taking tamoxifen were 18% more likely to survive without a recurrence than women who took them together.

In another study, women with early-stage breast cancer that had spread to several lymph nodes significantly cut the risk of recurrence simply by replacing one of the standard chemotherapy agents with a drug called docetaxel (Taxotere). By blocking cancer cells' division and growth process, docetaxel reduces the risk of tumor recurrence 50%.

And in a preliminary but promising finding in lung cancer, doctors discovered that a special form of vitamin A might reverse some of the changes in lung tissue caused by smoking. In a small study, former smokers who took the vitamin A derivative produced higher levels of a protein thought to be important in suppressing tumor growth than ex-smokers who took a placebo.

Because cancer research is moving quickly, it pays for cancer survivors—and their loved ones—to be vigilant. Think of cancer as a chronic condition, one you will have to stay on top of for the rest of your life. (This is also true for people at high risk for cancer who have been lucky enough to escape it so far.) Ask your doctor regularly if you're doing everything you can to keep the tumors at bay. The latest studies suggest that prevention really is the best medicine. ■

For more, visit www.asco.org *or e-mail* **alcpark@aol.com**

MAK STUDIO—ENVISION

NO BONES ABOUT IT Regular tea drinking may strengthen bones, say researchers in Taiwan. After surveying more than 1,000 men and women 30 and older, scientists found that people who drank an average of nearly two cups of tea—black, green or oolong—daily for 10 years had a 6.2% greater hip-bone density than occasional drinkers. Scientists suspect that fluoride, flavonoids and phytoestrogens—a few of the 4,000 health-affecting chemical compounds found in tea—may help preserve bone-mineral density.

ALZHEIMER'S HOPE? Researchers have discovered a substance that appears to prevent the formation of amyloid plaques, which are implicated in such diseases as Alzheimer's, amyloidosis and Type 2 diabetes. Doctors hope to start a clinical trial within weeks using the experimental drug CPHPC on Alzheimer's patients.

CINDERELLA SYNDROME It may be good for the soul, but researchers say housework doesn't do much for the heart. University of Bristol scientists studied 2,341 British women ages 60 to 79 and found that heavy housework—vacuuming, washing windows and floors—had no effect on their health or weight. Women who spent 2½ hours a week doing such chores may have burned extra calories but were neither less obese nor had lower resting heart rates than those who did no cleaning at all. —*By Sora Song*

Sources: *Archives of Internal Medicine; Nature; Journal of Epidemiology and Community Health*

PHOTOFEST

D/S-13.

Subject: Fwd[2]:Awareness
Date: Wed, 19 Sep 2001 11:36:33 -0400
From: pmehta@unicef.org (Pankaj Mehta)
To: chaya_mehta@hotmail.com, insaind@bir.vsnl.net.in, kajalbanik@hotmail.com, kbajracharya@unicefrosa.org.np, mdupar@yahoo.com, rsachdev@bigfoot.com, SOCHARA@VSNL.COM, uhoque@unicefrosa.org.np

Forward Header

Subject: Fwd:Awareness
Author: Rochita Talukdar
Date: 19-Sep-01 9:40 AM

This is Cancer Awareness Month

A handsome, middle-aged man walked quietly into the cafe and sat down. Before he ordered, he couldn't help but notice a group of younger men at the table next to him. It was obvious they were making fun of something about him, and it wasn't until he remembered he was wearing a small pink ribbon on the lapel of his suit that he became aware of what the joke was all about.

The man brushed off the reaction as ignorance, but the smirks began to get to him. He looked one of the rude men square in the eye, placed his hand beneath the ribbon and asked, quizzically, "This?"

With that the men all began to laugh out loud. The man he addressed said, as he fought back laughter, "Hey, sorry man, but we were just commenting on how pretty your little ribbon looks against your blue jacket!"

The middle aged man calmly motioned for the joker to come over to his table, and invited him to sit down. As uncomfortable as he was, the guy obliged, not really sure why. In a soft voice, the middle aged man said,

"I wear this ribbon to bring awareness about breast cancer. I wear it in my mother's honour".

"Oh, sorry dude. She died of breast cancer?"
"No, she didn't. She's alive and well. But her breasts nourished me as an infant, and were a soft resting place for my head when I was scared or lonely as a little boy. I'm very grateful for my mother's breasts, and her health."

"Umm," the stranger replied, "Yeah."
"And I wear this ribbon to honour my wife," the middle aged man went on.
"And she's okay, too?", the other guy asked.
"Oh, yes. She's fine. Her breasts have been a great source of loving pleasure for both of us, and with them she nurtured beautiful daughter 23 years ago. I am grateful for my wife's breasts, and for her health."
"Uh huh. And I guess you wear it to honour your daughter, also?"
"No. It's too late to honour my daughter by wearing it now. My daughter died of breast cancer one month ago. She thought she was too young to have breast cancer, so when she accidentally noticed a small lump, she ignored it. She thought that since it wasn't painful, it must not be anything to worry about."

Shaken and ashamed, the now sober stranger said, "Oh, man, I'm so sorry mister".

TN 9/19 9/19

To SKK/others → Library-Cancer File 9/19

So, in my daughter's memory, too, I proudly wear this little ribbon, which allows me the opportunity to enlighten others. Now, go home and talk to your wife and your daughters, your mother and your friends. And here . .

The middle-aged man reached in his pocket and handed the other man a little pink ribbon. The guy looked at it, slowly raised his head and asked, "Can ya help me put it on?"

This is breast cancer awareness month. Do regular breast self-exams and have annual mammograms if you are a woman over the age of 40. And encourage those women you love to do the same. Please send this on to anyone you would like to remind of the importance of breast cancer awareness.

A CANDLE LOSES NOTHING BY LIGHTING ANOTHER CANDLE, PLEASE KEEP THIS CANDLE GOING! This one I do ask that you send on.

Main Identity

From: "Erin Purvis" <mojxkpdd@yahoo.com>
To: <pwr@vsnl.com>
Cc: <sochara@vsnl.com>; <gai@vsnl.com>, <bhaskardk@vsnl.com>, <fortpapl@vsnl.com>, <sawalka@vsnl.com>; <vacation@vsnl.com>
Sent: Monday, December 01, 2003 9:36 PM
Subject: US STOCK MARKET - HTDS Medical Research---CANCER Trials.....ariana

US Stock Market - Stock Profile of the Week

Symbol: HTDS
Market: PK
Sector: MEDICAL RESEARCH

BARCHART Rates HTDS an 80% BUY - http://quotes.barchart.com/texpert.asp?sym=HTDS

Before we begin our profile we have very exciting, breaking news...

Tubercin Passes Toxicity Trials - Ready To Proceed To Live Cancer Trials

BREAKING NEWS - DELRAY BEACH, Fla.--(BUSINESS WIRE)--Hard to Treat Diseases Incorporated (Pink Sheets:HTDS) announces that Tubercin® has passed the toxicity tests required to proceed to the live cancer trials. Testing Tubercin® on live Melanoma, Lung and Breast cancer cells will begin immediately. The President and CEO, Mr. Colm J. King, met with the spokesperson of the medical group at their offices in Oklahoma City. Mr. King was advised that the tests were conducted under strict FDA (Federal Drug Administration) guidelines. Full test results will be available at the corporate offices as soon as the reports and findings are printed.

"These are the most promising results to date regarding Tubercin® and we're looking forward to additional positive results in the near future," stated Mr. King. "These tests prove that Tubercin® is non-toxic and is the first step on the way to human clinical trials as well as the first positive breakthrough conducted in the United States with an independent medical group for Tubercin®."

Operating out of Delray Beach, Florida, Hard to Treat Diseases Incorporated ("HTTD") holds the international marketing rights, except South Korea, to Tubercin®, a patented immunostimulant developed for combating Cancer under medical patent (US Patent 6,274,356). The unique properties unlike other cancer products are clearly stated in the abstract summary of the patent... "A carbohydrate complex, which is a mixture of low molecular-weight polysaccharides of an arabinomannan structure extracted from Mycobacterium tuberculosis, is highly effective in treating various cancer patients without incurring any adverse side effects."

STOCK PROFILE OF THE WEEK

HTDS is now at an emerging and potentially explosive stage. As stated in their press release, Tubercin is now ready to proceed (after tests conducted under strict FDA guidelines) to human clinical trials. While they have jumped one very big hurdle, they are still in the early stages of development and now is a great time for investors to take heed.

TUBERCIN

Over the past ten years, epoch making anticancer agents have continuously been introduced, but the mortality of cancer patients have been rising in the U.S. and the European countries not to mention Japan and Korea. The decisive measure to cope with cancer is surgery.

When the cancer cells spread throughout the body instead of remaining on the original spot, the treatment should take into consideration chemotherapy, radiation therapy and immunotherapy. The drawback of such therapies, however, is they incur damages not only on cancer cells, but also on the normal cells.

Chemotherapy and radiation therapy are not suitable for application on weakened patients, especially those above 70. Historically, various forms of immunotherapy have been performed, falling short of therapeutic expectation. When Bacille calmetteguerin is used as an active no-specific immunotherapeutic agent, however, the patient's prognosis turns better through a simulative action on immune system of the cancer case.

Professor T.H. Chung of Korea extracted carbohydrate complex Tubercin from microbacterium tuberculosis to be used as immunostimulant. This was meant to activate the T-lymphocyte of the cancer patient to produce lymphokine. This process strengthened and promoted immuno surveillance activities in deficient state and alieviated the pain and prolonged the life of cancer patients.

Of late the pharmaceutical industry in advanced countries started to put on the market so called cancer vaccines (active specific immunotherapy). The vaccines, bacterial extracts, as adjuvants, with autologous and or allogenic cancer cells to generate antibodies to cancer cells, facilitating the killer T-cells to recognize and destroy cancer cells.

The laboratory work to modify autologous or allogenic cancer cells are not ordinary and simple. When our lab work augments the active specific immunotherapeutic agents, the Tubercin will be one of the best adjuvants. Meanwhile, the main point of AIDS is its virus killing T-cells and Tubercin helps maintain healthy T-cells. Consequently, we focus our effort on the application of Tubercin to AIDS.

TUBERCIN is derived from micro bacterium tuberculosis. As an immunostimulant, TUBERCIN strengthens the human body's own immune system and assists the body in seeking out and combating cancer cells. HTTD is potentially able to develop TUBERCIN into a low-cost product to treat cancer patients on an international scale. Salient treatment, through the administration of TUBERCIN, could positively affect thousands of lives in North America. In addition, Europe and Asia have millions of lives at risk each year because of viral diseases such as cancer.

TUBERCIN IS A FINISHED PRODUCT. Tubercin as an immunostimulant has been administered to human patients in stages three and four of terminal cancer. There have been no indications of

any adverse side effects in human trials There has been encouraging results of patients with TUBERCIN in the last fourteen years. Various forms of cancer were involved and many of the patients survived.

A review of clinical studies indicate TUBERCIN has no side effects and could possibly be administered in conjunction with other such modalities for the treatment of cancer without any adverse effects. The scientific presumption would be the distinct possibility of a strengthened immunity system and the administration of treatment such as chemotherapy at the later stages of tumor growth would not be impeded by the weakened condition of the terminal cancer patient. To this end the Company has been assisted by outside consultants reviewing the research data and human trials involving TUBERCIN to see specifically whereby incidents of dual treatment produced favorable results in terms of moving toward indication of prolongation of the life of the cancer patient.

There is recognition that morphine is an trusted pain killer, but in totality it cannot be said that it has no side effects. In the maintaining of patient care, there is the strong possibility that TUBERCIN could be also considered as a candidate for a pain management. The Company's scientists describe TUBERCIN as having the high propensity of deadening the nerve endings in specific areas of the body where cancer has caused erosion and consequently much pain.

PATENTS

Presently, HTTD has the patent rights for Korea, Japan and the United States. The Korean patent was issued on October 29, 1998 (Registration No. 173362). The Japanese patent was issued on June 12, 1998 (Registration No. 2790447). The United States patent was issued on August 14, 2001 (Registration No.6,274,356). Currently, patents are pending for Canada and Europe (the United Kingdom, France, Germany, Italy and Spain).

CANCER IN OUR TIME

In the 20th century, the number of cancer patients has been on the increase. Although many anti-cancer agents were developed and an enormous study on its essence continued, the mortality by cancer still is increasing. Mankind may be chronically threatened with cancer in the 21st century. Nine million new case of cancer occur annually and five million people die from breast cancer, reports the World Health Organization. Dramatic increases in life expectancy and change in lifestyle are estimated to increase the number of new cancer cases to 20 million annually by 2020 and cancer deaths to more than 10 million.

About 552,200 Americans - more than 1,500 people a day - are excepted to die of cancer this year. In the United States, one of every four deaths is attributed to cancer. Cancer is the second-leading cause of death in the United States. Exceeded only by heart disease. About 5 million lives have been lost to cancer since 1990 and about 13 million new cases have been diagnosed. In 2000, more then 1.2 million new cancer cases are expected to be diagnosed. The number of cancer cases will continue to grow, spurred by the aging population. By 2009, this patient group could total 8.4 million. In 1997, about 6.3 million people worldwide died from some form of cancer, and most major international cancer agencies expect this number to double by 2022.

Please note that HTDS had absolutley nothing to do with this report and is not a participant in any way.

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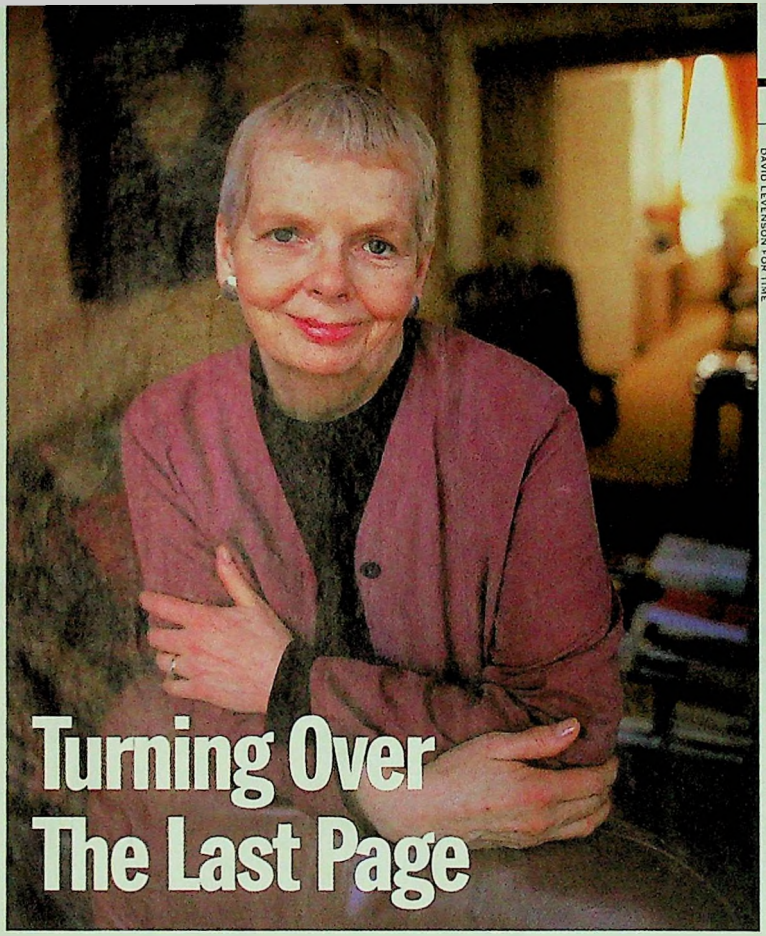


DAVID LEVENSON FOR TIME

SHINING SOUL: Being labeled a woman's writer "never worried me for a minute," Shields says. "It's an important thing to be"

Turning Over The Last Page

Dying of breast cancer, Carol Shields talks about her life, her illness and her superb new novel, *Unless*

By LEV GROSSMAN

"I KNEW I WANTED HER TO BE A WRITER," says Carol Shields. "I wanted her to be about 40 years old. I wanted her to live in a certain house. And I wanted something terrible to happen to her."

Perched on an overstuffed armchair that looks like it might swallow her whole, Shields is talking about Reta Winters, the heroine of her new novel, *Unless*, but she isn't being cruel—or if she is, it's because life itself is cruel. Shields needed something terrible to happen to Reta because something terrible was happening to her. Shields, 66, is dying of breast cancer, and *Unless* will be her last word.

She almost never wrote her first. The daughter of a factory manager from Oak Park, Illinois—the birthplace of Ernest Hemingway, the bard of brawn—the tiny, winsome Shields never imagined she could become a writer at all. "I thought it was like wanting to be a movie star!" she recalls. "I never thought writers could be people like me." Instead, she married Don Shields, an engineer, and moved to Canada, where she had five children in 10 years.

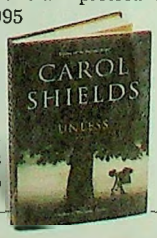
But when her last child marched off to kindergarten, something unexpected happened. "It was very hard to find novels at that time that had anything to do with my life," says Shields. "It was all about leaving your home, leaving your children, not *having* children. So I started writing the kinds of books that I wanted to read." Her first novel appeared when she was 40. With her eighth she accomplished that rarest of literary feats, a crossover hit: *The Stone Diaries* was an international best seller and a critical triumph, winning the 1995 Pulitzer Prize for fiction.

Last year, when she sat down to write *Unless*, Shields knew what she did not want: a cancer book. Instead, she wrote about Reta, a middle-aged novelist whose daughter Norah has abruptly dropped out of college to panhandle on a Toronto street corner. Norah won't speak; she wears a sign around her neck that reads, simply, GOODNESS. Reta is Shields' not-quite alter ego, and like Shields, she is discovering a realm of pain she never knew existed. "The whole sense of sadness, of the end of things, of the broken vessel—everything is there," says Shields in her quiet, serious voice.

Reta narrates her predicament in the first person, circling it doggedly, chattily, sometimes with a deliciously malicious wit, taking us inside her domestic routines, her comfortable, functional marriage, her kaffeeklatsch, her struggles with her own new book. (Along with everything else, *Unless* is rich with practical advice for the would-be novelist.) Shields swings easily from comedy to tragedy and back again—she says she doesn't really believe in the distinction anyway—pausing in between for a disquisition on the biology of the trilobite (a prehistoric creepy-crawly), an expert demolition of literary journalists (no offense taken) and an angry letter to a chauvinist academic.

But pain is never far: it's the book's frozen, icy core, and the most vivid moments in *Unless* demonstrate the oblique, unexpected angles at which agony can enter our lives—as when Reta impulsively scrawls MY HEART IS BROKEN in the ladies' room of a bar, or when she effortlessly encapsulates postholiday gloom with a single question: "Is there any task as joyless as undecorating a tree?" *Unless* isn't a grand finale to Shields' oeuvre; it's not a monumental summing up. It's a graceful coda, an arabesque performed over an abyss. Reta speaks to us in a voice both calm and urgent. This is no time for prevarication, she seems to say. This is the time for truth.

For Shields, time is growing short. Comfortably retired in an ivy-covered mansion in Victoria, British Columbia, she is wrapping up a few last obligations—a preface here, an essay there. She goes antiquing with her daughter, attends a local discussion group, answers e-mail. She tires easily, her face going gray with fatigue (her husband hovers protectively), and she still writes in a sunny upstairs study that used to be a sewing room. She is even considering an excursion into the sonnet. She will write as long as she can. As Reta puts it, "This matters, the remaking of an untenable world through the nib of a pen; it matters so much I can't stop doing it." ■



CANCER-GATE

How to Win the Losing Cancer War

Samuel S. Epstein, M.D.

BAYWOOD PUBLISHING COMPANY, INC.
AMITYVILLE, NEW YORK

In Praise *(Continued)*

There is less and less effort to inform workers and their families, and the general public, about avoidable environmental and occupational causes of cancer. This book will make you pause and think—especially if you have, or a loved one has, cancer.

Eula Bingham, Ph.D.
Professor Emerita of Environmental Health, University of Cincinnati Medical Center
Former Assistant Secretary of Labor, Occupational Safety and Health Administration

Dr. Epstein's factual exposé of the National Cancer Institute and American Cancer Society—their conflicts of interest, co-option by the pharmaceutical and petrochemical industries, and indifference to cancer prevention—is riveting. Dr. Epstein reaches for the law to turn the issue of public health into one of human rights. This book belongs on the bookshelf of every lawyer and teacher of environmental law or public health, in every law library, and on the reading lists of all law school classes.

George S. Grossman
Professor of Law and Director, Law Library, University of California, Davis

As *Cancer-Gate* details, the National Cancer Institute and American Cancer Society have narrowly focused their policies and resources on promoting highly profitable Big Pharma "miracle" drugs in largely unsuccessful efforts to cure cancer. What's more, in defiance of the Human Rights Covenants, they have denied the public its right to know of available information on the causes and prevention of cancer.

Dr. Rosalie Bertell
Former President, International Institute of Concern for Public Health
Member, National Association for Public Health Policy,
International Science Oversight Committee

Professor Epstein's scientifically accurate yet highly readable book is an extraordinarily important depiction of the failure of President Nixon's 1971 "War on Cancer." This has been due to concentration on highly questionable treatment and a monumental neglect of preventing environmental and other avoidable causes of cancer. Like the "War on Terrorism," which has been sidetracked into a war on Iraq and on human rights, the "War on Cancer" has enriched powerful special interests and stifled the free flow of public information. This book provides recommendations and inspiration for, at long last, transforming the largely futile, and inflationary, cancer war into realistic strategies to prevent the nation's leading cause of suffering and premature death.

Victor W. Sidel, M.D.
Distinguished University Professor of Social Medicine,
Montefiore Medical Center/Albert Einstein College of Medicine
Past President, American Public Health Association

Cancer has surpassed heart disease as America's #1 killer, but the National Cancer Institute continues to hope that miraculous "magic bullets" will save us. For more than three decades, Prof. Samuel S. Epstein has shown that many kinds of cancer can be prevented by simply eliminating carcinogens in the air, food, water, and workplace. Vested interests have blocked this strategy. Sam Epstein is a national treasure and his *Cancer-Gate* is simply magnificent—a battle cry for activists to reclaim the failing war against cancer.

Ralph W. Moss, Ph.D.
President, Cancer Communications, Inc., Lemont, Pennsylvania
Director, *The Moss Reports*, and Author, *The Cancer Industry*

Dr. Epstein is a scientist/scholar/activist who devotes his life 24/7 to informing the public about what really causes cancer, and how we can protect ourselves. In this brilliant and compelling book, in spite of the silence of the National Cancer Institute and attacks by industry, he has established guidelines on the public's undeniable right to know about avoidable causes of cancer in the environment, workplace, hormone replacement therapy and other prescription drugs, and consumer products.

Barbara Seaman
Co-Founder, National Women's Health Network
Author, *The Doctor's Case Against the Pill*

Cancer-Gate is Dr. Epstein's heroic effort to show us how to reduce our risks of cancer. Motivated by compassion and concern, he does not fail to deeply impress. In both print and film, he is as remarkable in his command of scientific data as in his ability to present them in a way that is both convincing to the public health community and accessible to the general public. He has shared these powerful insights in my recent documentary, *The Corporation*.

Mark Achbar
Executive Producer and Co-Director, *The Corporation*
Recipient of 22 international awards

Dr. Epstein's new masterpiece, *Cancer-Gate*, takes the onus from an industry that tries to keep us in the dark about the war on cancer and puts the information right into our hands. This well-researched book acts as a roadmap, showing what is being done and what can be done regarding the war on cancer. The importance of becoming proactive gets even more personal as Dr. Epstein reveals the role that the cosmetics industry plays in the cancer epidemic, in my forthcoming documentary *America the Beautiful*.

Darryl Roberts
Producer, Sensory Overload Productions

Table of Contents

About the Author

Dr. Epstein, Professor Emeritus of Environmental and Occupational Medicine at the School of Public Health, University of Illinois at Chicago, and Chairman of the Cancer Prevention Coalition, is an internationally recognized authority on the causes and prevention of cancer. He has published some 270 scientific articles and 11 books, including the prize-winning *The Politics of Cancer* (1978), *The Safe Shopper's Bible* (1995), *The Breast Cancer Prevention Program* and *The Politics of Cancer Revisited* (both 1998). His popular writings include numerous press releases, and op-eds and letters in leading newspapers. Dr. Epstein also has extensive media experience. He is the recipient of many prizes and awards, and a member of the National Writers Union, AFL-CIO, and National Association of Science Writers.

About the Book

Cancer-Gate's *searing indictment of the National Cancer Institute (NCI) and American Cancer Society (ACS) for losing the war against cancer, launched by President Nixon in 1971, has been endorsed by over 100 leading independent scientific experts in cancer prevention and public health, including past directors of federal research and regulatory agencies, besides citizen activist groups.*

Despite decades of false assurances, we are losing the winnable war against cancer. The hand-in-glove generals of the federal NCI and the "nonprofit" ACS have betrayed us. These institutions have spent tens of billions of taxpayer and charity dollars, largely promoting ineffective drugs for terminal disease, while virtually ignoring strategies for preventing cancer, other than quitting smoking. As a result, cancer rates have escalated to epidemic proportions, now striking nearly one in two men and more than one in three women. Paradoxically, the more we spend on fighting cancer, the more cancer we seem to get.

But, as *Cancer-Gate* shows, there is much more. In particular, the NCI and ACS are rife with institutional, and even personal, conflicts of interest with the cancer drug industry. For the ACS, these conflicts extend flagrantly to the chemical industry. Unbelievably, PR for the ACS is handled by Edelman, whose major clients are the tobacco and fast food and beverage industries.

Cancer-Gate details how the NCI and ACS are sitting on mountains of information on environmental and other avoidable causes of cancer, while failing to act on this and make it available to Congress and the public. This silence even extends to frank suppression of information.

Cancer-Gate explains how we can win the war against cancer with strategies including "right-to-know" laws, ensuring public dissemination of critical information on environmental carcinogens and other avoidable causes of cancer, and Congressional reform and oversight to ensure that the NCI protects the public rather than special interests.

Finally, *Cancer-Gate* tells you, the reader, how to fight back by arming yourself with the information you need to protect your family from everyday carcinogens, and how to become an activist in the war against cancer.

In Praise

Dr. Epstein penetrates the facades of the huge cancer institutions and organizations and explodes the myth that they are protecting us from cancer-causing agents. In *Cancer-Gate*, he demonstrates that he is a fearless fighter in the battle against environmental carcinogens.

Ruth Winter
Past President, American Society of Journalists and Authors

Relentlessly, and with meticulous documentation, Dr. Epstein updates us on the unresponsiveness of the National Cancer Institute and American Cancer Society to avoidable causes of cancer. His urgent message—stop cancer before it starts—is daily more imperative and must be heeded. This book is a must for every public health student and professional.

Quentin D. Young, M.D.
Chairman, Health and Medicine Policy Research Group
Past President, American Public Health Association

Dr. Epstein is a legend in the field of cancer prevention. From his 1978 *The Politics of Cancer* through this latest brilliant work, *Cancer-Gate*, Epstein demonstrates a clear understanding of the cancer crisis and the only real solution—cancer prevention. This year, 1,400,000 Americans will be diagnosed with cancer and 600,000 will die. If we had taken Epstein's advice on cancer prevention 30 years ago we would not be facing this tragedy today.

Frank D. Wiewel
Founder, People Against Cancer

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