patients how they felt that diarrhoea had affected their lifestyle. The frequency of attacks is obviously important but is by no means the only factor to be considered. Most patients with diarrhoea emphasised that it was the sudden, unpredictable onset of the attacks that they minded most. On close questioning it became apparent that the urgency preceding an attack of diarrhoea could be so intense that some patients had actually been incontinent. The fear of being embarrassed in a public place was common, and it was obvious that this fear often dominated the patient's lifestyle.[11] A patient who experienced only one attack a week could be as incapacitated as a patient with daily attacks, depending on their circumstances. Many patients with persistent postvagotomy diarrhoea are labelled neurotic, but the anxiety they show may be a secondary phenomenon, rather than due to an underlying psychological abnormality.[12] We were disturbed to find patients who had lost their jobs or had to change them because of diarrhoea. We also found that patients with physical disabilities were particularly badly affected, even infrequent attacks resulting in incontinence.

Most surgeons believe that postvagotomy diarrhoea disappears with time. Many gastric surgery patients experience a short period of diarrhoea after the operation, which settles spontaneously; this may have led to a false complacency. Our study confirms that postvagotomy diarrhoea does not disappear with time, and we believe there is little improvement with time. The prognosis for the patient in whom this side-effect develops is, therefore, not good.

Ulcer recurrence is widely regarded as being the ultimate failure of ulcer surgery, but since the introduction of the H_2-receptor antagonists this may no longer be true. Postvagotomy diarrhoea may be more difficult to treat than ulcer recurrence; many of our patients found standard treatments ineffective. We are now carrying out a study of treatments for postvagotomy diarrhoea; nearly all patients have had relief of diarrhoea with once-daily loperamide (to be published elsewhere). However, any treatment for this disorder would be required for the rest of the patient's life.

40 years ago diarrhoea may have seemed a worthwhile price to pay for safe and effective ulcer-healing. However, there are now operations virtually free of functional side-effects.[13,14] We believe it is difficult to justify the continued use of truncal vagotomy and drainage and conclude that the risk of diarrhoea is sufficient reason to avoid this type of operation whenever possible.

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Drug Evaluation

USELESS DRUGS ARE NOT PLACEBOS: LESSONS FROM FLUNARIZINE AND CINNARIZINE

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A PAPER by Chouza et al[1] on extrapyramidal signs and depression induced by flunarizine raises doubts about the safety of cinnarizine. Flunarizine, a difluorinated derivative of cinnarizine, was marketed at the beginning of the 1980s, 12–14 years after cinnarizine.

In certain European countries cinnarizine is widely prescribed for "chronic cerebrovascular disease". Within Europe the prescription of "cerebral vasodilators" is perhaps greatest in Spain, even though other countries have a higher proportion of old people in their populations. In 1985 8 million units of preparations containing cinnarizine were prescribed, and in Spain 5–7% of the population over the age of 60 may be on long-term cinnarizine. In 1984 the total value of prescriptions of pharmaceutical products containing cinnarizine and issued by the Spanish social security system was 6200 million pesetas (about $43·5 million). By contrast, cinnarizine is not even on the market in the USA, and in Europe its use varies widely.

It is not surprising, then, that extrapyramidal signs attributed to cinnarizine were first reported from Spain. In 1985 Martí Massó et al[2] described eleven patients aged 65–83 in whom parkinsonism developed after treatment with cinnarizine for from 6 to more than 36 months at daily doses of 150 mg. Subsequently Martí Massó reported a double-blind, placebo controlled randomised trial of cinnarizine 150 mg daily in 20 patients with mildly incapacitating Parkinson's disease.[3] After 1 month, 4 of the 10 patients in the cinnarizine group had to be withdrawn from the study because of worsening of their condition; Webster's score and other objective scores and indicators significantly deteriorated in the cinnarizine-treated group.

Data on the pharmacokinetics of cinnarizine are scarce. Although no information is available for elderly people, it seems that the drug's plasma half-life in young volunteers is about 3 h.[4] By contrast, flunarizine has an elimination half-life of 4–19 days and is much more lipophilic,[5] suggesting that it is more likely to accumulate and cause CNS effects. The main indication for cinnarizine is "cerebral arteriosclerosis" but randomised trials of cinnarizine have been inconclusive, mainly because inclusion criteria and outcome variables have not been well specified.[6] Nor is the evidence for the efficacy of other drugs used as cerebral vasodilators convincing.[7]

S. A. RAIMES AND OTHERS: REFERENCES—*continued*

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SUSPECTED EXTRAPYRAMIDAL ADVERSE EFFECTS OF CINNARIZINE AND FLUNARIZINE (WHO COLLABORATING DRUG MONITORING PROGRAMME)*

Age sex	Suspected drug†	Daily dose	Duration of treatment	Suspected adverse drug reaction‡	Improved with dechallenge
78/M	C	. .	4·5 yr	ED + T	. .
46/F	C	45	5 days	ED	No
48/F	C	. .	14 mo	T	. .
68/M	C	150	2 days	T	Yes
73/M	C	150	. .§	T	Yes
69/F	C	150	. .	AP	No
64/F	C	60–180	1 yr	T	No
68/M	C	150	2 days	T	Yes
64/F	F	10	28 days	AP	Yes
42/M	F	10	4 mo	T	Yes
48/F	F	20	11 days	T	No
60/F	F	10	6 wk	T	Yes
68/M	F	10	1 yr	ED	Yes
69/F	F	10	8 mo	ED	No

*There is some delay in reporting from national centres to the WHO Collaborating Centre, Uppsala, so numbers are not up to date.
†C = cinnarizine; F = flunarizine.
‡ED = extrapyramidal disorder, T = tremor, AP = aggravated parkinsonism.
§It is certain that cinnarizine intake began before the tremor.
. . = unknown.

Cinnarizine is mainly prescribed to old people with intellectual impairment and/or focal neurological signs, in whom extrapyramidal signs may easily be attributed to spontaneous deterioration rather than drug-induced parkinsonism. This may be why so few cases were notified through the spontaneous reporting system that has been operating in Catalonia since 1983: of 7 adverse drug reactions attributed to cinnarizine, 5 were extrapyramidal symptoms. The WHO International Drug Monitoring Programme's file in Uppsala contains 3 further reports of extrapyramidal disorders and tremor associated with cinnarizine (table) and 6 reports of extrapyramidal disorders associated with flunarizine. The accompanying table shows that extrapyramidal symptoms do occur at the recommended daily flunarizine dose of 10 mg, even in young patients, contradicting Amery's points[8] about Chouza's paper.[1]

Cinnarizine, flunarizine, and drugs with a similar spectrum of indications (eg, co-dergocrine and citicoline) are used as "mass placebos" in some countries. The successful marketing of these useless drugs—which are not even mentioned in most pharmacology textbooks—suggests that prescribers either accept the claims made by manufacturers, being unable to conceive that a registered drug can lack efficacy, or, while sceptical about those claims, mistakenly believe that a drug without any proven benefit will at least be safe.

Sulocticil, another "cerebral vasodilator" recommended for cerebral and peripheral ischaemia, was withdrawn in 1985 because it was found to induce hepatitis, in some cases fatally. Another dangerous "placebo" withdrawn in 1985 was cyanidanol, promoted as a hepatoprotective agent for the treatment of hepatitis B and other liver diseases. Cases of haemolytic anaemia, some fatal, were ascribed to it.

The main side-effect of placebos, however, is not likely to be uncovered by any drug surveillance system. Misused placebos may produce the false sensation, among doctors and patients, that some treatment is being provided when in fact nothing is being done except delay the diagnosis and treatment of the disease underlying the patient's symptoms. The very existence of these drugs, promoted as all-purpose remedies for the elderly, constitutes an invitation to prescribe them for every such patient in an irrational way by spinal reflex prescription rather than by rational drug prescription.

Why are drugs of this kind available in important pharmaceutical markets in Western Europe? Drug registration authorities evaluating a new product will look at efficacy and safety. If there is no benefit demonstrated and the drug carries risks, the benefit/risk ratio is zero, and the drug should not be on the market, especially if it is to be paid for with public money through a national health or social security scheme. The registration of drugs of no proven efficacy is potentially dangerous. Such drugs should be banned, and national health authorities should adopt clear criteria for the evaluation of drug efficacy.

We thank the national drug monitoring centres of Belgium (Dr Ph. Janssens), West Germany (Dr G. Kreutz), Ireland (Dr A. I. Scott), Italy (Prof L. Rossini and Prof L. Leone), and the Netherlands (Dr R. H. B. Meyboom) for permission to use their data.

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Point of View

STROKES IN MILD HYPERTENSION: DIASTOLIC RULES

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Fisher[1] has reviewed evidence suggesting that the risk of cardiovascular disease is related more closely to systolic than to diastolic blood pressure, and suggested that routine measurement of diastolic blood pressure could be abandoned. The report of the Medical Research Council trial of treatment of mild hypertension[2] appears to give some support to this view. It stated that systolic blood pressure at entry to the trial was significantly associated with the subsequent development of strokes and all cardiovascular complications, whereas diastolic pressure at entry was less clearly related to the risk of complications. This conclusion was certainly incorrect for strokes, as will be shown below, and may also be incorrect for other cardiovascular complications.

The MRC report also stated that there was no relation between systolic or diastolic blood pressure at entry to the study and the percentage reduction in stroke incidence with active antihypertensive treatment, and it concluded that the benefits of treatment were uniform over the range of blood pressure studied. This conclusion is also incorrect. The benefits of preventive treatment have to be assessed in

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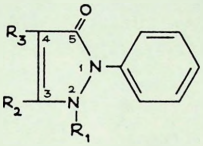
Meyers & Jawetz / Goldfien 1978

Table 27–2. Pyrazolone analgesics.



	R_1	R_2	R_3
Antipyrine	$-CH_3$	$-CH_3$	$-H$
Aminopyrine (amidopyrine)	$-CH_3$	$-CH_3$	$-N(CH_3)_2$
Dipyrone (aminopyrinesulfonate, methampyrone)	$-CH_3$	$-CH_3$	$-N(CH_3)-CH_2-SO_3Na$
Phenylbutazone (Butazolidin)	–phenyl	–OH	$-C_4H_9$
Oxyphenbutazone (Tandearil)	–*p*-hydroxyphenyl	–OH	$-C_4H_9$
Sulfinpyrazone (Anturane)*	–phenyl	–OH	$-C_2H_4-SO-$phenyl

*Uricosuric agent discussed in Chapter 40.

ated in the body to oxyphenbutazone, and this metabolite is also available as a drug.

Antipyrine is slowly metabolized by hydroxylation at liver microsomes, with a half-life of about 8 hours. Phenylbutazone and oxyphenbutazone are even more slowly metabolized and are well reabsorbed by the renal tubules, resulting in a half-life in excess of 2 days.

Sulfinpyrazone (Anturane), the metabolite of a compound closely related to phenylbutazone, is a very useful uricosuric agent.

Pharmacologic Effects

The therapeutic effects are similar to those of aspirin—ie, these drugs are analgesic, antipyretic, and anti-inflammatory.

Clinical Uses & Dosages

The pyrazolone drugs exert an antipyretic effect in some situations in which aspirin is not completely effective—eg, Hodgkin's disease with fever unresponsive to salicylates or chemotherapy. They are probably also more potent as analgesics and anti-inflammatory agents in arthritis, bursitis, and thrombophlebitis. There is no justification for the use of aminopyrine or dipyrone.

A. Antipyrine: Antipyrine can be used orally, 0.3–0.6 gm every 4–6 hours, as an alternative to aspirin. The volume of distribution of antipyrine or its metabolite, N-acetyl-4-aminoantipyrine, may also be used to measure total body water.

B. Phenylbutazone (Butazolidin) and Oxyphenbutazone (Tandearil): Butazolidin, Tandearil, and Butazolidin Alka are among the 200 drugs most commonly prescribed by physicians in the USA, suggesting that they are often used as first treatment drugs rather than as alternatives to aspirin. Yet the restrictions on their use and the contraindications and cautions made a part of the labeling by the manufacturer are so strin-

Table 27–3. Pyrazolone derivatives: Dosages and preparations available.

	Usual Adult Dose	Preparations Available
Aminopyrine*	300–600 mg/day	Bulk powder
Antipyrine	300–600 mg every 4 hours	Bulk powder
Dipyrone (Pyrilgin, Narone)*	325–650 mg every 4–6 hours	Tablets, 325, 500, and 650 mg Oral liquid, 500 mg/5 ml Pediatric liquid, 250 mg/ml Injection (IM), 500 mg, 2, 10, and 30 ml
Phenylbutazone (Butazolidin)	100 mg 3–4 times daily	Tablets, 100 mg Capsules (Butazolidin Alka), 100 mg, with antacids
Oxyphenbutazone (Tandearil)	100 mg 3–4 times daily	Tablets, 100 mg

*Not recommended for any use. See text.

gent and comprehensive that responsibility for any adverse result of therapy would probably devolve on the physician. The drugs should not be used without reference to the package insert.

The use of these drugs is suggested or permitted in acute rheumatoid arthritis or spondylitis, osteoarthritis, psoriatic arthritis, "painful shoulder," acute superficial thrombophlebitis, and acute gouty arthritis.

The daily dose is stated to be 300–600 mg/day by the labeling. A more conservative position limits the daily dose to 200 mg. These drugs should be discontinued if no improvement is observed in 4–5 days.

Adverse Reactions

The toxicity of the pyrazolone analgesics restricts their use.

A. Antipyrine: Antipyrine causes fewer side-effects than aspirin. Unlike aminopyrine, it has rarely been associated with agranulocytosis. It has caused an allergic erythematous rash, often about the mouth, that leaves pigmented areas when it resolves.

B. Agranulocytosis From Aminopyrine and Dipyrone: The unusually high risk of agranulocytosis following the use of these 2 analgesics is generally acknowledged. As is true for many therapeutic agents, the quantification of the risk is difficult, and the drugs continue to be used in some countries. Neither of the drugs was used recently in the USA until dipyrone reappeared during the period 1960–1964. Imports of dipyrone rose from none in 1958 to 19,000 lb in 1962. During the period 1960–1964, 18 cases of agranulocytosis associated with the use of dipyrone, one-third of them fatal, were reported to the AMA registry. How complete this reporting was cannot be established. The dipyrone was probably not recognized by the physician as a derivative of aminopyrine, emphasizing the need to think of drugs in terms of general classes rather than individual compounds. The use of drugs under their trade names and the prescribing of proprietary mixtures without first identifying the ingredients undoubtedly also led to the misuse.

In the USA, any preparation or mixture containing aminopyrine or dipyrone must now bear a label warning that the drug may cause agranulocytosis and that it should be used only when specifically indicated and when less toxic drugs—eg, salicylates—have proved ineffective or are not tolerated.

The characteristics of agranulocytosis are discussed in Chapter 6. The reaction is allergic in origin rather than dose-related and is due to the sudden peripheral destruction of granulocytes.

C. Phenylbutazone: Phenylbutazone and its metabolite, oxyphenbutazone, frequently cause side-effects, and serious toxic reactions are frequent enough that their use should be greatly restricted. Dose-related toxic effects include sodium retention and edema, dry mouth, nausea and vomiting, peptic ulceration and hemorrhage, and rare cases of renal tubular necrosis and liver necrosis. Allergic reactions include dermatitis, which may rarely progress to exfoliative dermatitis, and agranulocytosis.

Phenylbutazone may cause a reversible leukemoid reaction; of greater concern, however, is the possibility (not yet well established) that its chronic use may be associated with a high incidence of acute leukemia.

Administration of phenylbutazone increases the effects of tolbutamide and warfarin.

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Phenacetin & Acetaminophen

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The Pharmac. basis of Therapeutics
Goodman & Gilman 5th Ed 1975.

NOL). Official preparations include tablets (120 and 325 mg) and an elixir and syrup (120 mg/5 ml); a solution (60 mg/0.6 ml) is also available.

The conventional oral dosage is 325 to 650 mg every 4 hours for adults and older children. The total daily dose should not exceed 2.6 g. For young children, the single dose is 60 to 120 mg, depending upon age and weight; total daily dosage should not exceed 1.2 g. Acetaminophen should not be administered for more than 10 days or to young children except upon advice of a physician.

Phenacetin (*acetophenetidin*) is no longer an official drug. It is too insoluble to be prescribed in aqueous solution, and is usually administered orally in powder, capsule, or tablet form. In recent years it has been employed primarily in analgesic mixtures. The average single dose for adults is 300 mg; the total daily dose should not exceed 2.4 g.

Therapeutic Uses. Acetaminophen or phenacetin is a suitable substitute for aspirin for its analgesic or antipyretic uses in patients who are allergic to aspirin or when aspirin is contraindicated, as in patients with gout or peptic ulcer. Acetaminophen has somewhat less overall toxicity and is preferred over phenacetin. Neither drug is an effective antirheumatic agent. An additional minor convenience of acetaminophen is its availability in a liquid dosage form for oral ingestion.

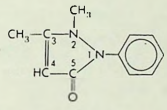
Analgesia. For headache, dysmenorrhea, arthralgia, myalgia, and similar disorders, a therapeutic dose of acetaminophen or phenacetin may be given every 3 or 4 hours. Self-medication over a period of days is not advised. If ordinary doses are ineffective, larger amounts as a rule do not give relief. Acetaminophen is definitely less effective than aspirin in patients with active rheumatoid arthritis, and any relief obtained is due to the analgesic effect. Analgesic combinations containing acetaminophen and phenacetin are discussed below.

Antipyresis. The use of acetaminophen or phenacetin to reduce fever is similar to that of aspirin. The indications and the rationale for reducing body temperature are discussed in connection with the salicylates.

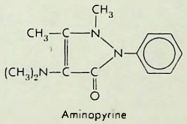
PYRAZOLON DERIVATIVES: ANTIPYRINE AND AMINOPYRINE

Antipyrine (*phenazone*) and *aminopyrine* (*amidopyrine*) were introduced into medicine in the late nineteenth century as antipyretics and subsequently were also widely used as analgesics and anti-inflammatory agents. However, clinical use of aminopyrine was sharply curtailed after its potentially fatal bone-marrow toxicity was recognized, and antipyrine has also lost favor. Both drugs have virtually disappeared from the therapeutic scene in the United States, but antipyrine is still employed in some countries, usually in analgesic mixtures. A variety of related pyrazolon derivatives have enjoyed sporadic popularity. The congeneric phenylbutazone has limited usefulness as an anti-inflammatory agent (*see* above).

Chemistry and Pharmacological Properties. Antipyrine and aminopyrine are closely related phenylpyrazolon derivatives. Their structural formulas are as follows:



Antipyrine



Aminopyrine

The pharmacology and toxicology of antipyrine and aminopyrine have been reviewed by Greenberg (1950), Randall (1963), and Beaver (1965, 1966). In both animals and man, the pyrazolon derivatives exhibit *analgesic*, *antipyretic*, and *anti-inflammatory* properties similar to those of the salicylates. Neither antipyrine nor aminopyrine has been subjected to adequately controlled clinical trial by current standards. However, aminopyrine was considered the superior anti-inflammatory agent and equivalent to aspirin for therapy of acute rheumatic fever. Unlike salicylate, the pyrazolon derivatives are not organic acids, are only slightly bound to plasma protein, and do not have uricosuric properties. They do not cause gastric irritation or produce the acid-base or metabolic effects of salicylate.

Aminopyrine Agranulocytosis. Aminopyrine and its close congener *dipyrone* cause a high incidence of agranulocytosis. This allergic reaction is characterized by the presence in the plasma of antibodies to granulocytes (*see* Wintrobe, 1969). In rare individuals, instead of frank agranulocytosis, each administration of aminopyrine produces a sharp fall in total leukocyte count associated with a severe chill, spiking fever, headache, and pain in muscles and joints; the attack is over within a few hours. The incidence of aminopyrine-induced agranulocytosis has been variously estimated between 0.01 and 0.86%. The mortality rate has been 20 to 50% (*see* Huguley, 1964).

Antipyrine. Reports of agranulocytosis attributed to antipyrine have been rare. Nevertheless, because it is closely related to aminopyrine and because it is not superior to safer drugs, the use of antipyrine as an analgesic and antipyretic is not recommended. Whether antipyrine has clinically useful antirheu-

matic properties has never been adequately determined. It is no longer an official drug.

Antipyrine is employed as a *pharmacological tool* for measurement of total body water and for assessment of hepatic microsomal mixed-function oxidase activity. It is rapidly and essentially completely absorbed from the gastrointestinal tract. Peak plasma concentration is usually attained in 1 to 2 hours. It is less than 10% bound to plasma proteins and is distributed in various tissues in proportion to their water content. About 30 to 40% of the drug is converted to 4-hydroxyantipyrine. This metabolite is rapidly and almost completely conjugated with glucuronic, and perhaps sulfuric, acid and excreted in the urine. Only about 5% of unaltered antipyrine is eliminated in the urine. Hydroxylation of the side chain also occurs, but the fate of a significant fraction of the drug remains uncertain. The plasma half-time for the unchanged drug is 7 to 20 hours (*see* Brodie and Axelrod, 1950).

Antipyrine causes induction of the hepatic microsomal enzyme system and modifies the biotransformation of other drugs, including the oral anticoagulant agents.

Aminopyrine and Dipyrone. "Over-the-counter" sale of *aminopyrine* in the United States has been prohibited since 1938, and federal regulations require that preparations of aminopyrine and dipyrone bear a warning on the labels stating that *the drug may cause fatal agranulocytosis.*

Although it is an excellent antipyretic, analgesic, and anti-inflammatory agent, and despite its advantages over salicylate, *aminopyrine* ordinarily should not be employed because of the danger of agranulocytosis. In some cases of prolonged intractable fever, as in Hodgkin's disease and periarteritis nodosa, aminopyrine is capable of controlling the disability and may be justified. *Dipyrone*, the methanesulfonate derivative of aminopyrine, has similar pharmacological and toxicological properties, including the potential to cause fatal agranulocytosis. It differs only in being more soluble and available for parenteral administration.

If used at all in the treatment of intractable fever, aminopyrine or dipyrone should be employed only after safer drugs and other measures have proven ineffective, and only with proper supervision and monitoring. Administration of dipyrone with chlorpromazine can result in serious hypothermia, and such use is contraindicated. Dipyrone can aggravate a bleeding tendency or prothrombin deficiency.

SALICYLAMIDE

Salicylamide, the amide of salicylic acid, is no longer an official drug. Its effects in man are not reliable, and its use is not recommended. The small doses included in "over-the-counter" analgesic and sedative mixtures are probably ineffective.

Although not metabolized to salicylate in the body, salicylamide has antipyretic, analgesic, and anti-inflammatory effects similar to those of salicylate. It also has sedative and hypotensive effects. However, the drug is very rapidly inactivated during absorption and the initial circulation through the liver. Concentrations of active drug in the systemic circulation are markedly influenced by the dosage form, and they are disproportionately low after low doses. Salicylamide may inhibit the metabolism of other drugs by the liver.

ANALGESIC COMBINATIONS AND MIXTURES

Aspirin, acetaminophen, and phenacetin are frequently administered with each other and a variety of other drugs, including caffeine, sedatives, and the opioid analgesics. Concurrent administration of an opioid and an analgesic-antipyretic, such as codeine and aspirin, has a valid role in analgesic medication. However, none of the mixtures of analgesic-antipyretics, including the traditional aspirin-phenacetin-caffeine combination, has been shown to provide significant advantage over medication with aspirin alone.

Irrational analgesic mixtures, such as those with a hazardous component or presumed active ingredients that are in fact inert, can be expected to disappear from the therapeutic scene when the assessment of "over-the-counter" medications currently being conducted by the FDA is completed and the recommendations of its panel are implemented.

Combined Opioid and Analgesic-Antipyretic Medication. In most controlled clinical trials, codeine, 65 mg, has been found to add significantly to the analgesic effect of aspirin, 650 mg. The combined codeine-aspirin effect can be duplicated by larger doses of codeine alone, but considerations of toxicity and abuse favor restricting the dosage of the opioid. Thus, combined codeine-aspirin analgesia is justified if aspirin alone in full dosage is ineffective. Gastrointestinal and central side effects typical of the opioids are the price for the increased analgesia provided by this multiple-drug therapy. Parenteral opioids are still required for relief of severe pain.

In adequate dosage, other orally effective opioids add similarly to the analgesic effect of aspirin. In general, a dose of an opioid that given alone provides uncertain analgesia adds only equivocally to the analgesic effect of aspirin. Although it is likely that an effective dose of an opioid adds to the analgesic effect of acetaminophen as it does to that of aspirin, clinical documentation is required. The usual arguments for and against the use of fixed-dose mixtures versus concurrent but separate administration of the components apply to combined opioid and analgesic-antipyretic medication (*see* Chapter 1).

State of the Art/Review

Therese Southgate, MD, *Section Editor*

Rational Therapeutic Drug Monitoring

Friedman, MD, D. J. Greenblatt, MD

FOR MANY drugs, the measurement of concentrations in serum or plasma has become widely available and is accepted as an important component of clinical decision making. While these assay levels often do allow more effective monitoring and titration of therapy, the information also has the potential to be valueless or even misleading. Laboratories sometimes report that a serum concentration is in the "toxic" range, when the patient is doing well and has no evidence of toxic effects. Or, conversely, the drug is not detectable in serum. Such discrepancies between measured serum drug concentrations and observed clinical drug effects may occur for numerous reasons. This article will review some principles and problems associated with therapeutic drug monitoring.

RATIONALE FOR MONITORING SERUM DRUG LEVELS

For a serum drug concentration to be potentially useful for purposes of therapeutic monitoring, at least two requirements must be fulfilled.[1] First, the serum drug concentration must reflect the concentration at the receptor site; second, the intensity and duration of the pharmacodynamic effect must be temporally correlated with the receptor site drug concentration. When these two conditions are not met, as in the case of anticancer drugs showing effects long after they are gone from the serum, the likelihood of correlating serum levels with therapeutic effect is considerably reduced.

During long-term dosage with any drug, the two major determinants of its mean steady-state serum concentration are the rate at which the drug is administered (dosing rate) and the drug's total clearance in that particular patient.[2,3] The mathematical relationship is

$$\text{Mean Steady-State Concentration} = \frac{\text{Dosing Rate}}{\text{Clearance}}$$

Clearance is measured in units of volume per unit of time, and describes in quantitative terms the capacity of a given individual to biotransform or eliminate a given drug. Drug clearance is usually accomplished by hepatic biotransformation, renal excretion, or a combination of the two. Thus, under usual circumstances, the steady-state concentration of a particular drug in a given individual is directly proportional to the dosing rate (with the exception of a few drugs with saturable or nonlinear kinetics, such as salicylate, phenytoin, and alcohol). Among different individuals, however, any given dosing rate is likely to produce wide variations in steady-state concentration, attributable to large interindividual differences in clearance (Fig 1). A number of identifiable factors can alter the clearance of drugs, such as age, gender, body habitus, disease states, cigarette smoking, and drug interactions.[2-9] However, substantial unexplained individual variation in drug clearance is commonly observed even among healthy, drug-free persons of the same sex and within a narrow age range.[10] Therefore, dosage may not be a good predictor of steady-state concentration.

"Therapeutic range" and "therapeutic index" are two concepts used to quantitate the relationships of serum concentration to efficacy and safety, respectively. Some drugs have a well-defined therapeutic range. When the steady-state concentration falls within this range, the likelihood of clinically effective and nontoxic therapy is maximized. Direct measurement of the serum concentration allows appropriate upward or downward titration of dosage in the individual patient, to attain the desired level. Therapeutic ranges, however, are not absolute (Fig 2). Levels at the "low" therapeutic end have a significant likelihood of being clinically ineffective, whereas levels at the high therapeutic end have a significant likelihood of causing toxic effects.

In experimental pharmacology, "therapeutic index" is defined as the ratio of the median lethal dose to the median effective dose. In clinical medicine, however, therapeutic index is usually estimated as the ratio of the highest potentially therapeutic concentration divided by the lowest potentially therapeutic concentration (Fig 2). Some drugs (such as gentamicin, digoxin, and lithium) have a narrow therapeutic range and therefore a low therapeutic index. For such drugs, one can anticipate considerable overlap among ineffective, effective, and possibly toxic concentrations, thereby increasing the importance of serum level monitoring.

Serum drug concentrations may still be of considerable value even when a therapeutic range has not been definitely established. Consider a patient with no apparent clinical response to drug therapy despite seemingly adequate dosage. A measured steady-state concentration that appropriately reflects the dosage rate suggests that the patient may actually be a "nonresponder." If, however, the measured level is very low or undetectable, this suggests that the patient either is not taking the medication (noncompliance) or has unusually high metabolic clearance. Another example is the patient with a sign or symptom (such as loss of appetite during digitalis therapy) that could be attributable either to an adverse drug reaction or to the underlying disease itself.[11] In this case, a high serum drug level suggests that the medication might be responsible for the adverse effect; a low serum level, on the other hand, could indicate that the underlying disease, or some other factor, explains the reaction.

Drug concentrations frequently are measured for medicolegal reasons. In cases of deliberate or accidental drug overdosage, verification of the particular substances ingested, and their concentrations in serum, may have important therapeutic and forensic value. "Screening" of current and prospective employees for the presence of "illicit drugs" is becoming increasingly common, although these tests are usually done on samples of urine.[12]

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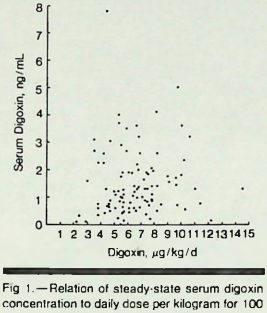


Fig 1.—Relation of steady-state serum digoxin concentration to daily dose per kilogram for 100 patients receiving long-term digoxin therapy. Correlation is poor ($r = .069$), indicating substantial variability in steady-state concentration that is not explained by dosage (Hermann R. Ochs, MD, unpublished data, 1979).

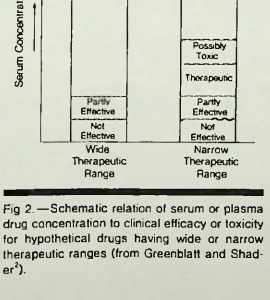


Fig 2.—Schematic relation of serum or plasma drug concentration to clinical efficacy or toxicity for hypothetical drugs having wide or narrow therapeutic ranges (from Greenblatt and Shader[4]).

Finally, the availability of methods for measurement of drug concentrations provides the impetus for clinicians to increase their expertise and understanding of pharmacologic and pharmacokinetic principles of drug therapy. Enhanced awareness of dose-concentration relationships, and factors influencing these relationships, may lead to an overall improvement in the quality of drug treatment.[13]

DRUG DISTRIBUTION AND ACCESS TO ITS RECEPTOR

When a drug is given by an extravascular route of administration (orally, intramuscularly, rectally, subcutaneously, sublingually, transdermally, etc), or even by intravenous injection, the entire administered dose does not have immediate and complete access to its receptor site mediating pharmacologic activity (Fig 3). After intravenous injection, the entire dose reaches the systemic circulation and by definition has 100% bioavailability. However, the drug is distributed not only to the tissue where it is active, but also to a number of other sites (Fig 4). Furthermore, once the drug has reached the systemic circulation, it also encounters serum or plasma proteins. Drugs are bound to proteins to varying degrees.[14,15] The principal binding proteins are albumin and α_1-acid glycoprotein. The affinity of a drug for serum protein limits its freedom to diffuse across cell membranes, hence further limiting its accessibility to the receptor site.

When a drug is administered by an extravascular route, it reaches the systemic circulation indirectly, often yielding less than 100% bioavailability.[16] Oral bioavailability of drugs in tablet and capsule form can be influenced by incomplete absorption due to incomplete dissolution, which in turn depends on packaging and drug particle size. Oral solutions overcome the dissolution problem. Other factors that can influence oral bioavailability include changes in gastrointestinal motility, gastric and intestinal pH, malabsorption syndromes, and the coadministration of foods and drugs (especially antacids, antidiarrheal agents, and chelating agents).

After absorption of the drug from the gastrointestinal tract, systemic bioavailability may be reduced because of metabolic transformation in the gut wall, or by extraction from the portal circulation during the "first pass" through the liver. This is the case for certain drugs characterized by high hepatic clearance, including propranolol, lidocaine, tricyclic antidepressants, opiate analgesics, neuroleptics, hydralazine, nitroglycerin, verapamil, and prednisone.[17]

Incomplete bioavailability after intramuscular injection is also possible. This has been attributed to poor drug solubility at physiologic pH and precipitation at the injection site after administration of chlordiazepoxide, digoxin, phenylbutazone, phenytoin, and quinidine.[18]

A number of recent studies have evaluated drug absorption after sublingual or buccal administration.[19-21] In principle, this route of administration delivers the drug directly into the systemic circulation, bypassing both the gastrointestinal tract, where some drugs are degraded or metabolized, and the portal circulation and consequent first-pass hepatic extraction. For most drugs evaluated to date, bioavailability after sublingual dosage is equivalent to or greater than that after oral administration. A similar principle holds for rectal drug administration, since approximately 50% of the hemorrhoidal circulation empties into the systemic rather than the portal venous system.[22] Finally, the transdermal[23] or pulmonary route can be used to administer some drugs.

For all these reasons, drug concentrations in blood, serum, or plasma often reflect pharmacologic action more closely than administered dosage alone.

FACTORS INFLUENCING INTERPRETATION OF SERUM DRUG CONCENTRATIONS

Total vs Free Serum Concentrations

Although only the unbound or free drug can passively cross cell membranes and interact with receptors, free drug levels nonetheless are still not routinely monitored. This is partly because their measurement is technically more difficult to perform than that of total levels. Fortunately, for most drugs, the ratio of free to total serum concentration (free fraction) usually remains relatively constant during a given patient's course of therapy, with salicylate and ibuprofen[24,25] being among notable exceptions. Therefore, a doubling of the total concentration will also lead to a doubling of the free serum drug concentration at steady state. In most clinical circumstances, variability *between* patients in free fraction may also be relatively small.[26] When within- and between-individual differences in serum protein binding are small, monitoring of total serum concentration should prove to be as useful therapeutically as monitoring of free or unbound concentration.[15,27-29] In some conditions, however, drug binding to serum protein may be substantially altered. For example, protein binding of a given drug may be reduced (increased free fraction) when another drug displaces it from its binding sites.[15,28] Such interactions in themselves are unlikely to be of direct clinical importance,[15,27-29,30] since the increased "free" concentrations will be only transient due to rapid equilibration with tissues. However, the total drug concentration will consequently fall, and may lead to a lowering of the therapeutic and toxic ranges for the total serum drug level (Fig 5).[31] Uremia and hypoalbuminemia are other clini-

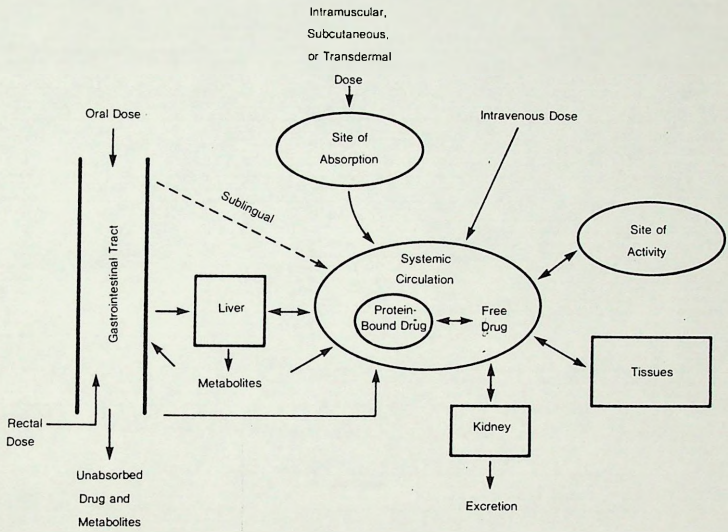


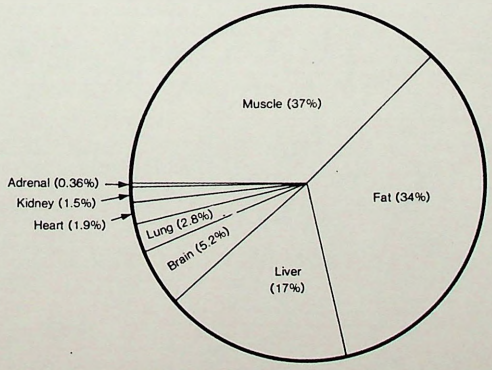
Fig 3.—Schematic diagram of pathways of drug absorption, distribution, elimination, and clearance.

ral situations in which serum protein binding of drugs is reduced, causing lowered therapeutic and toxic ranges for total drug concentration. For example, phenytoin free fraction, which usually falls between 10% and 20%, may become as high as 30% in uremics.[31] Alternatively, α_1-acid glycoprotein, an acute phase reactant, may be transiently elevated in acute myocardial infarction, shock, severe burns, injuries, or infectious processes,[32] causing *increased* binding of some basic drugs, and result in increased total serum drug levels without an enhancement of clinical effect. Examples of such drugs include lidocaine, propranolol, imipramine, phenytoin, quinidine, and disopyramide. For drugs not extensively bound to serum proteins, such as cimetidine, digoxin, and gentamicin, lithium, procainamide and acecainamide (N-acetylprocainamide), changes in protein binding are of far less consequence.

Optimal Sample Timing

Proper choice of sampling time is crucial for the interpretation of serum

Fig 4.—Estimated distribution pattern of benzodiazepine derivative nordazepam (desmethyldiazepam) in normal healthy woman (30% body fat), based on human autopsy studies.[47] Nordazepam (desmethyldiazepam) is major metabolite of diazepam (Valium) and halazepam (Paxipam), and is principal active substance present in blood during treatment with clorazepate dipotassium (Tranxene) and prazepam (Centrax).



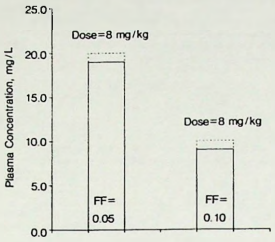


Fig 5.—Influence of change in protein binding on total and unbound serum or plasma concentrations of hypothetical drug at steady state. It is assumed that drug is being administered at constant dosing rate (8 mg/kg/d), and that drug's total clearance is also constant. When free fraction (FF) is 0.05 (left), total plasma drug concentration is 20 mg/L, and free concentration is 1.0 mg/L (dotted lines). If for some reason extent of protein binding is reduced, and FF is increased to 0.10 (right), steady-state free drug concentration remains at 1.0 mg/L because there has been no change in either dosing rate or clearance. However, *total* concentration falls to 10 mg/L. Thus, change in protein binding (free fraction) by itself causes no alteration in free drug concentration, but will cause reciprocal change in total drug concentration (from Greenblatt and Shader[2]).

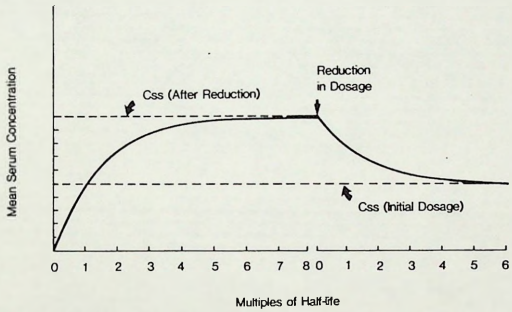
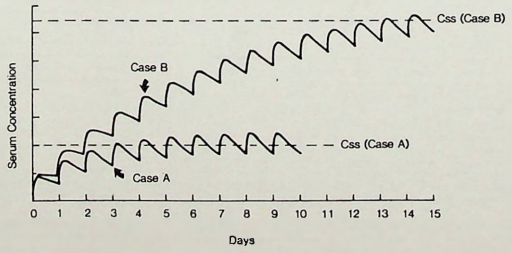


Fig 6.—Time course (in multiples of half-life) of mean serum concentration during attainment of steady-state condition after starting therapy and after reducing dosage. Css indicates mean serum concentration at steady state (from Greenblatt and Shader[2]).

Fig 7.—Time course of attainment of steady-state condition, assuming drug is given once daily. Case A indicates drug with short half-life; case B, drug with long half-life (from Greenblatt and Shader[2]).



drug concentrations. In general, it takes four times the drug's half-life at a constant dosing rate for the steady-state condition to be more than 90% attained. Similarly, an increase or decrease in dosage will require the same time interval to reach the new steady-state level (Fig 6). After initiating therapy with long half-life drugs, a considerable length of time may be required for steady state to be attained (Fig 7). Therefore, sampling before the attainment of the actual steady-state condition may lead to premature dosage adjustments. This is of particular importance for drugs such as theophylline that are administered to infants and children.

Occasionally, the need may arise to hasten the attainment of therapeutic concentrations. This can be achieved by giving an initial loading dose, the size of which has been appropriately chosen based on the desired therapeutic concentration and the pharmacokinetic characteristics of the drug.[2,14] However, even the ideally selected loading dose has potential disadvantages. The rapid attainment of therapeutic concentrations precludes gradual adaptation to therapeutic or adverse drug effects, such as sedative, hypotensive, bradycardic, or anticholinergic properties.

Once the steady-state condition has been achieved, the mean steady-state serum drug level should remain constant as long as the dosing rate and clearance are constant (as indicated in the equation in the first section of this article). However, the interdose fluctuation depends on the dosage interval. A proportional increase or decrease in both the size of each dose and the interval between doses, such that the overall dosing rate remains constant, does not change the mean steady-state concentration, but will alter the interdose fluctuation (Fig 8). More frequent

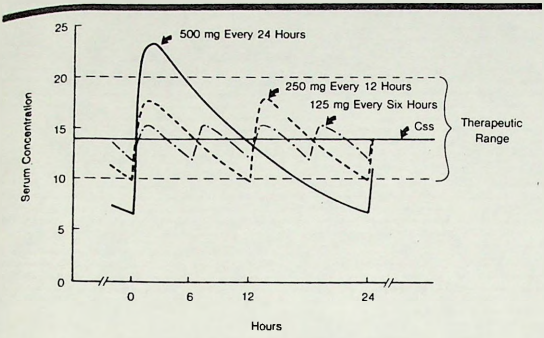


Fig 8.—Interdose fluctuation of serum drug concentration as function of dosage schedule, assuming that drug is given in overall total dosage of 500 mg/24 h, but with different dosing schedules. Note that mean serum concentration at steady state (Css) is same for each regimen, and that interdose fluctuation is largest for once-daily therapy (from Greenblatt and Shader[2]).

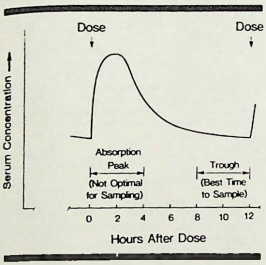


Fig 9.—Time course of serum drug concentration at steady state during oral dosage every 12 hours, with illustration of optimal sampling time (from Greenblatt and Shader[2]).

dosing is useful to minimize transient effects due to high peak levels that some people find objectionable, such as sedation and drowsiness from certain psychotropic drugs.[35] On the other hand, dosing schedules that require very frequent dosing are inconvenient, and may be associated with reduced patient compliance.

Certain sustained-release formulations of drugs have been designed to prolong drug action after each dose, thereby allowing less frequent dosing. If the rate of drug entry into the systemic circulation precisely mimics a fixed-rate infusion, then the serum drug level will not fluctuate. Although this is not an attainable ideal, some sustained-release preparations do in fact allow infrequent dosing, with only small fluctuations in serum drug concentrations.[36]

At steady state, each discrete drug dose is followed by an "absorptive" phase, during which serum concentrations exceed the mean. Transient side effects may be associated with the absorptive peak. After peak concentrations are reached, the serum level then falls as distribution and clearance predominate. Just before the next dose, levels are at a minimum during the "trough" phase. Sampling shortly after a dose, during the absorptive phase, is not recommended for evaluation of therapeutic efficacy since the measured level does not necessarily correspond to the peak. Furthermore, even if the peak level was found to be in the therapeutic dosing range, this would not ensure therapeutic levels throughout the entire dosage interval. The optimal time to sample for evaluation of efficacy is just before the time of dosing (Fig 9), to ensure that the minimum drug level falls with the therapeutic range. If the trough level is found to be subtherapeutic, the clinician may elect to give smaller doses more frequently while maintaining the same total dose per 24 hours (Fig 8). This change would reduce the interdose fluctuation and possibly bring the trough level to within the therapeutic range. Measurement of peak serum concentrations after an individual dose may be of value when clinicians wish to evaluate potential drug side effects coinciding with peak concentrations. Knowledge of both peak and trough concentrations may be desirable for drugs with narrow therapeutic indexes, such as aminoglycosides or lithium. Unfortunately, however, the time of peak concentration can seldom be predicted with certainty.

If the dosage interval is not regular, or if the drug is taken intermittently, then the best time to sample is not necessarily so obvious, since there is no single "trough" concentration (Fig 10).

Artefacts due to Collection Tubes

The Vacutainer brand of blood collection tubes is reported to contain TRIS (2-butoxyethyl) phosphate, a plasticizing agent. Blood samples drawn into these tubes can give spuriously low serum drug levels when the serum is analyzed for imipramine, alprenolol, propranolol, lidocaine, and quinidine.[32] The mechanism for the lowering of serum levels appears to involve displacement of drugs from α_1-acid glycoprotein (but not from albumin) by TRIS (2-butoxyethyl) phosphate. This in vitro phenomenon results in an increase in unbound drug, which quickly diffuses into and equilibrates with the red blood cells present in the tube. Thus, when the serum is aspirated after centrifugation, the resultant serum drug level is spuriously low. However, the whole blood level is unchanged. Any drug that is extensively bound to α_1-acid glycoprotein is likely to be influenced by this collection artefact.

Analytic Methodology

Knowledge of the methodology used by a laboratory in analyzing serum for drug levels may be of critical importance for the clinician in interpreting the results. Ideally, an assay procedure for a particular drug should (1) resolve compounds of similar structure, such as the parent drug and its metabolic products or other substances present in the serum (specificity); (2) consistently conform to accepted standards for accuracy and replicability for the range of concentrations encountered clinically; and (3) be sensitive enough to quantitate levels well below the therapeutic range. In addition, the need for cost containment must always be considered. Procedurally straightforward analytic methods that can be automated are generally less expensive and therefore preferred. However, such procedures, although less costly, may not provide adequate specificity, accuracy, replicability, and sensitivity. More complex and often more expensive analytic methods may be needed to provide meaningful serum concentration data.

Historically, spectrophotometry and

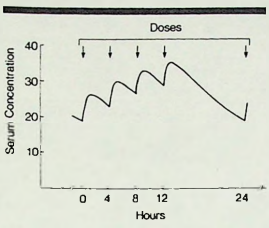


Fig 10.—Plasma concentrations of drug at steady state with four-times-daily dosing schedule, with individual doses given at times shown by arrows. This complex dosing schedule makes monitoring of plasma drug levels more difficult (from Greenblatt and Shader[2]).

colorimetry were the first methods widely used in laboratories for measurement of drug levels.[37] These procedures may require one or more solvent extractions, often coupled with chemical reactions, to yield a solution containing primarily the drug of interest. The absorption of visible, infrared, or ultraviolet light at a specific wavelength by the drug in solution is used to quantitate its presence. The level of sensitivity is usually on the order of parts per million to parts per thousand. These methods are limited by poor sensitivity and variable specificity,[17] and high cost.

Immunoassays for drugs have become popular within the last 20 years.[38] In principle, they rely on the interaction between a drug acting as an antigen and an antibody to it. Since most drugs are nonimmunogenic, they first must be conjugated by a bridge or linkage group to a substance of high molecular weight, such as a protein. In this conjugated mode, the drug behaves like a hapten and is used to immunize an animal. Antibodies may be generated against the drug if the conjugation bridge or linkage keeps the drug sufficiently far from the larger protein molecule. The necessity for an antibody to seek out a hapten creates the inherent variability in specificity provided by immunoassays. Some antibodies may show cross-reactivity with metabolites and congeners of the drug of interest, thereby rendering the antibodies relatively nonspecific.[39]

In the radioimmunoassay (RIA), drug present in a serum sample competes with a radioisotope-labeled ligand for antibody binding sites. The RIA procedures are stated to be very sensitive, but require the use of radioactive material and are costly. Enzyme immunoassays substitute an enzymatic label for a radioactive one. The inhibition of labeled enzyme activity by antibody is the basis for the very popular enzyme-multiplied immunoassay technique. This technique is claimed to be procedurally straightforward and inexpensive, but is considerably less sensitive than RIA and can have variable specificity, particularly when applied to screening for drugs of abuse in urine.[12,40,41] Most nonisotopic immunoassay labels are inactivated by antibody; hence, they do not require the separation of bound from free labeled ligand as in RIA.

Chromatography is a method of separating mixtures of substances based on their physicochemical characteristics, so that one or more of those substances may be specifically detected. The principal methods used in drug measurement are gas-liquid chromatography (GLC)[42] and high-pressure liquid chromatography (HPLC).[43] Serum, or a concentrated extract thereof, is injected onto a column through which flows a mobile phase. For GLC, the mobile phase is a purified gas such as helium, nitrogen, or argon. For HPLC, the mobile phase contains mixtures of an aqueous buffer and an organic solvent such as acetonitrile or methanol. Separation of the serum components by the mobile phase is influenced by interactions with the column's stationary phase. Actual separations are based on lipophilicity, polarity, molecular size, temperature, and boiling point (for GLC). The HPLC separations may be further refined by varying the pH and polarity of the mobile phase. Often it is possible to detect and quantitate the parent drug and some or all of its important metabolites simultaneously.

For some applications, a mass spectrometer is coupled to a chromatograph's effluent and thereby acts as the detector. This combination provides the "gold standard" in specificity and sensitivity in drug analysis. However, mass spectroscopy is expensive and requires complex instrumentation as well as highly trained personnel. When the drug mixture is well separated chromatographically, other less complex detection systems usually suffice. In GLC, the most commonly used detectors are flame ionization, nitrogen-phosphorus, and electron capture. Flame ionization will respond to all organic compounds. Nitrogen-phosphorus has enhanced response to nitrogen- and phosphorus-containing compounds, and electron capture responds to drug-containing electronegative substituents such as halogens, nitrates, and conjugated carbonyls. The sensitivity of nitrogen-phosphorus and electron capture is in the subparts-per-billion range; that of flame ionization is on the order of parts per million. High-pressure liquid chromatography most commonly utilizes spectrophotometry, fluorescence, or electrochemistry for the detection and quantitation of drugs after chromatographic separation. Fluorescence detection is applicable to molecules with rigid polyaromatic structures or extensive conjugation having the property of absorbing light and then emitting it at a lower wavelength. Electrochemical detection is employed for the recognition of easily oxidized or reduced groups such as phenols, indoles, and secondary and tertiary nitrogens. In favorable cases, fluorescence and electrochemical detection can extend sensitivity two orders of magnitude beyond the spectrophotometric range.

The above information can be extremely useful to clinicians in interpreting serum drug concentration reports. Consider, for example, a "nondetectable" serum concentration report. This must be interpreted in light of the lower limits of sensitivity of the particular assay technique. If the assay technique has a high degree of sensitivity, a reported zero level may actually mean that there is no drug present in serum. Conversely, it may imply that clinically important amounts of drug may be present in serum, but the assay is not sufficiently sensitive to quantitate levels in this range. At the other extreme, laboratories may report very high serum drug concentrations in a patient taking "usual doses" and having no manifestations of toxicity. This might be attributable to the use of a very nonspecific assay technique that quantitates not only the drug in question but also its metabolic products, or possibly other endogenous unrelated substances present in serum. Finally, laboratories may report widely discrepant serum drug concentrations from day to day in samples drawn under identical conditions in a given patient receiving a constant dose of a drug. These variations could be due to variability over time in the patient's metabolic clearance or extent of drug absorption. They could also be attributable to insufficient accuracy in the laboratory determination, regardless of the method.

Laboratories should readily provide to any inquiring physician all details of analytic quality control procedures. Nonetheless, clinicians have means at their disposal to test and compare the performance of laboratories. If a pure reference standard of the drug in ques-

tion is available, physicians may "spike" drug-free control serum with various known concentrations of drug, and send them "blindly" to the laboratory. This procedure should provide information on the sensitivity and accuracy of the laboratory's methodology. Another procedure that can be used to test the replicability of determinations either within the same laboratory or between laboratories is to split a given serum sample into two aliquots. The aliquots can be then sent to different laboratories and the results compared. Alternatively, the same divided sample under different designations can be sent to the same laboratory on different days. The laboratory should quantitate the identical or nearly identical results in these split samples. When results on identical samples differ by less than 10%, the laboratory performance under these circumstances is acceptable.

Parent Drugs and Active Metabolites

Many drugs used in clinical practice are biotransformed into other compounds that themselves are pharmacologically active.[44,45] When evaluating the therapeutic effects of such drugs, clinicians must integrate the relative contributions of all active substances present in serum. Physicians should be knowledgeable of the metabolism of the drugs they prescribe, and analytic laboratories should automatically measure concentrations of parent drug and active metabolites. Consider, for example, a patient taking imipramine, which is biotransformed to the active metabolite desipramine. Clinicians requesting a serum imipramine concentration should expect, and laboratories should provide, simultaneous concentrations of both imipramine and desipramine present in the sample. In a few years, this problem may become further complicated by the appreciation of other active metabolites of imipramine, such as hydroxyimipramine and hydroxydesipramine.[46]

SUMMARY

The simple act of ordering a serum drug level does not guarantee that the information will be meaningful or useful. The interpretation of serum concentrations can be profoundly influenced by such factors as the timing of the sample, the patient's clinical state, the drug's pharmacokinetics and metabolism, and the tube type and analytic methodology used. The likelihood of obtaining clinically meaningful and useful results can be maximized when these factors are taken into account.

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Fallacy

DOES PERITONITIS IN THE UPPER ABDOMEN CAUSE PAIN IN THE TIP OF THE SHOULDER?

A WISE student soon learns that he can save himself effort by coupling understanding with fact. This is a great help where embryology, anatomy, and clinical signs can be linked. Pain—in particular referred pain—lends itself to this approach. We soon learn, for example, that colic from the ureter radiates to the groin and does not cross the midline because each side of the urinary tract has a multisegmental unilateral origin. We are therefore tempted, having found such relations, to apply the process in reverse. Since the heart and diaphragm originate from the cervical septum intermedium, which descends to the centre and lower part of the chest, we would expect referred pain in the area supplied by the cervical nerves. Coronary occlusion frequently causes arm pain, so we expect irritation of the diaphragm to do the same. Nowadays we see basal pleurisy infrequently, but in the past it was common, caused by pneumococcal and tuberculous infection. As we expect, there is shoulder tip pain with such disease.

We could assume that if irritation of one side of the diaphragm gives shoulder tip pain, the same symptom would arise from inflammation (peritonitis) on the abdominal side. This is what is commonly taught. However, only part of the diaphragm has a cervical origin. The rest is costal in derivation. The central or cervical area is not greatly exposed to the main peritoneal cavity. Most of all the right side is protected by the liver, which also has a large bare area. The greater part of the left side is isolated from the main cavity by the spleen, stomach, liver, and the reflections of the lesser sac. The most exposed part is that which is costal in origin, even when the peritoneal cavity contains gas and acid. Therefore, the pain is seldom referred to the shoulder tip: instead it is referred to the lower chest area. When the patient with a perforated ulcer is asked to sit up, pain between the scapulae is almost invariably present, whereas pain in the shoulder is very rare.

Thus if a patient has pain suggestive of a diaphragmatic lesion and the pain is referred to the tip of the shoulder, we should direct our attention more to the chest and its contents than to the abdomen.

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Therapeutics

DANGEROUS AND INAPPROPRIATE DRUGS

Competition between manufacturers in flourishing economic systems is said to benefit the consumer by way of cheaper and better products. This may be true when, say, television sets are being sold in sophisticated markets where the consumer has a good idea of what he wants and needs. The argument crumbles when the buyer has an imperfect understanding of the virtues and vices of what is on offer. In Western industrialised countries the ordinary citizen perceives, if somewhat dimly, what medicines can offer, but is nevertheless prey to plausible suggestions. He is therefore likely to take on trust that, because some aspects of health screening are useful in some people, there may be wider benefits to all—thus fostering a growing and often virtueless industry in wellperson screening. He will accept advice to buy branded products when the non-proprietary versions differ not at all, except in price, and he will assume that, because substances are labelled as health foods, herbal remedies, and homoeopathic remedies that they are indeed valuable. Some protection is available through the activities of drug regulatory and consumer advisory bodies, but there remains a wide and perhaps growing trend towards the promotion of costly practices which vary from the mildly deceptive to the frankly fraudulent.

Underdeveloped countries are beset by greater difficulties. They are ill placed to afford expensive but useless health care products, let alone the frankly dangerous. They have unsophisticated consumers and tend to have poorly developed regulatory and advisory systems. Against this background it is hardly surprising that pharmaceutical manufacturers, both international and indigenous, have indulged in practices which would be obviously unacceptable in Western countries. The World Health Organisation essential drugs list is a straightforward attempt to draw attention to the virtues of a limited range of generally cheap drugs, but it has so far failed to secure the widespread acceptance it deserves.

Health Action International has lately issued a compendium[1] of leaflets which detail the depressingly widespread tendency to peddle dangerous and inappropriate drugs in poor countries. It draws attention, for example, to the widespread continued availability of phenylbutazone and oxyphenbutazone as treatments for mild self-limiting painful conditions, of chloramphenicol in the management of minor infective disease, often of a nature unlikely to be responsive, and of antidiarrhoeals, when water and electrolyte replenishment represent prime needs.

The Health Action International pack on problem drugs covers nine areas: antidiarrhoeals, cough and cold remedies, growth stimulants, antibiotics, contraceptives, potency drugs, analgesics, drugs in pregnancy, and combination drugs. Each section contains dismal records of inappropriate and dangerous merchandising. The papers are individually referenced, but often to obscure sources which readers, even in developed countries, will find it impossible to examine (such as newspaper articles). The pattern of writing is direct, emphatic, and even strident, but given the list of

1. Prepared by Andrew Chetley and David Gilbert and published by the International Organisation of Consumers Unions, Emmastraat 9, 2595 EG The Hague, Netherlands.

unsupportable actions it catalogues this tone is understandable. The recommendations are generally clear, entirely acceptable, and obviously necessary (rehydration therapy before the use of antidiarrhoeals, ban oxyquinolines, cold cures do not work), but they could sometimes be better framed. Thus the recommendations for action on butazones are really part of an extended (and appropriate) diatribe, but lose force by being buried in the text; and the recommendations about contraceptives stem not from drug problems but problems of society (the second of HAI's recommendations here is to improve the status of women).

Virtuous as the Health Action International pack may be, a more important approach might be directed at the vested interests, not necessarily within the pharmaceutical industry, which perpetuate such a sorry state of affairs.

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In England Now

THE great debate of the moment is, of course, whether or not the Health Service is sufficiently funded. The Government—that is to say, the Prime Minister—speaking ex cathedra, assures us, in tones that brook no argument, that it is better funded than ever before in its history.

But those of us at the business end, both as providers and consumers, are not convinced. If money is adequate, why are wards being closed? Why are nurses' homes being sold off, on the wholly fallacious theory that, in future, any girl wishing to take up nursing can jolly well do it in her home town? Why, as in our hospital, does a secretary, when requiring a new pen, have to go to the Unit Admin Office, between 9.30 and 10 on a Tuesday, carrying the old one with her to effect an exchange? Why . . . oh, why go on? We are told, firmly, that things are fine and all of these problems must be but figments of our imagination. Can we not see that the Emperor is wearing the most beautiful suit of clothes?

No, we cannot. However, let us, in all charity, assume that the figures do show that, in real terms, more money *is* going into the NHS, and ask *where* it is going, as patient care plummets. An awful lot must go into administration. Now, fair enough, administrators are necessary, but is not the very substantial tail now wagging the weak and emaciated dog? Look at the money that is spent (wasted?) every few years in "reorganisation". Salmon. Area and District Management Teams. Scrap the Area tier. Now Griffiths—down with consensus, bring back despotism. Yet all of these schemes have cost vast sums of money and certainly all have led to a proliferation of the numbers of people not actually involved in patient care. The latest changes are no exception. Every general manager must have deputies; every chief must have his personal Admiral Byng who can be shot on his own quarterdeck if things go wrong "pour encourager les autres". Of course, we are told, this reorganisation is *the* answer, which will streamline the National Health Service and maximise resources into patient care. I have heard this before—several times. This time it is the importation of fresh managerial blood which will do the trick. This, perhaps, is the last of the old quaint English eccentricities—that if you want something done, you appoint someone with no knowledge of the subject. Provided a man was a gentleman—and preferably an officer as well—he could be a magistrate and know no law, rule an empire, and know nothing of the culture he ruled. Many of the new managers are ex-servicemen. Is running a health district really no different from running a small RAF station or a minor ordnance depot? Are the accounts really the same as keeping an eye on the junior officers' mess bills?

* * *

WE all heaved a sigh of relief when, at long last, Donald passed his finals. In those far-off days, every medical year had one—a student who always struggled on the brink of dissolution. No examination was ever passed at the first attempt and it was usually only at the third or fourth try that success finally rewarded effort. Indeed, with Donald, success was achieved mostly because we all rallied round to tutor him. After graduation he disappeared into an overworked practice in one of our underdeveloped areas.

Our paths failed to cross until I met him again at our 30th year reunion. He was impeccably dressed in a Savile Row suit and his Rolls Royce was parked rather ostentatiously outside the hotel entrance. He gave three cases of champagne to the chairman to help with the jollification.

During the cocktails, conversation, and canapés phase we fell to talking. His Harley Street practice was doing nicely, thank you very much. He attributed his success to the fact that he had discovered a new disease, and this had made him popular. I lifted my eyebrows, inquiringly. Yes, he said, it consisted of headache, backache, mild depression, and an urge to talk to someone for about 15 minutes or so. It particularly affected middle-aged women. But what had really made his name was a feature never before described. Indeed, when he told his patients of his finding, they were horrified that all the other doctors had missed it. "You know those funny sounds you hear through the stethoscope when you take a blood pressure?" he said. I agreed cautiously. "Well," continued Donald. "I found in every case, without exception, that the diastolic blood pressure was always higher than the systolic."

* * *

AM I alone in thinking that this Christian name business is getting out of hand? I know that we are, in the NHS, supposed to be one happy family, but do we have to go around using first names all of the time as part of the pretence?

I have always written my clinical letters to "Dear Dr Bloggs", never "Dear Jim". At first, all the Bloggses used to be older than me, and I would have felt it rude and presumptuous to be familiar. Now the tables are turned; most of the Bloggses are but veritable children, and I do not wish them to be familiar, so I retain the formality.

Now everyone expects instant intimacy. Junior administrators, still with marked post-auricular dampness, take it for granted they can use my Christian name, and are offended by the careful "Mr" I employ for them. Even nursing officers seem to consider it their right to call consultants by their first names, and to be so addressed in return. It is, I suppose, all part of the quaint fallacy that, to work together, we must all be chums ("and you shall call me Eric"), whereas it is easier to work with people about whom you are neutral and with whom you maintain a polite formality.

It all reaches its heights (or depths) with patients. I have for years been fighting a losing battle against the practice of automatically calling patients by their first names. The retired professional lady, called "Miss Jones" all her life, does not want, I am sure, to have chits of girls calling her "Molly". Then there is the old man, always called "Mr Smith" by his wife in public, or "Dad" in the family circle, who suddenly finds complete strangers calling him "Jack". Mind, I have to concede that the use of first names is, marginally, better than "Gran" or "Pops" or whatever other totally demeaning soubriquet the young happen to favour for the elderly at the time. But how much nicer would "Miss Jones" or "Mr Smith" be—more dignified, more respecting of individuality, all those things to which modern-day nurses pay lip service but ignore in practice.

Council on Drugs

Agranulocytosis Induced by Dipyrone, a Hazardous Antipyretic and Analgesic

Charles M. Huguley, Jr., MD, Atlanta

AN INCREASING NUMBER of reports of agranulocytosis associated with dipyrone are being received by the American Medical Association's Registry on Adverse Reactions. Between 1955 and 1959 only ten cases of leukopenia associated with this drug had been reported to the Registry from the United States, and none of these were in children. Since 1960, reports of 18 cases have been received, seven of them in children. Thirty-six percent of these patients have died. Since it is probable that many more cases of agranulocytosis occur than are reported to the Registry, these data are a cause for concern.

During the same period there has been a striking increase in the use of dipyrone. Much of the dipyrone used in this country is imported; domestic production and sales figures are not available, but US Tariff Commission figures show that imports increased from none in 1958, to 220 lb in 1959; 7,164 lb in 1960; 39,790 lb in 1961; and 18,879 lb in 1962. This increase in the use of dipyrone is puzzling, since the drug has the same pharmacological effects and therapeutic indications as aminopyrine, of which it is a derivative. Aminopyrine, on the other hand, does not seem to be in frequent use in this country, and only seven cases of leukopenia associated with aminopyrine have been reported to the Registry from the US since 1954. It may be suspected that many physicians who prescribe dipyrone are unaware of its relationship to aminopyrine.[1,2]

Some of the brands of aminopyrine and dipyrone available in the US today are listed in the Table. It has been suggested in England that no prescription for a drug or compound containing aminopyrine or its salts be valid unless the prescriber has indicated that it contains aminopyrine,[3] and astonishment has been expressed that these drugs are still being produced.[4] At this time, therefore, it seems in order to review briefly the history of these drugs and their relationship to agranulocytosis.

From Emory University School of Medicine.
This article was written at the request of the Council's Section on Adverse Reactions.

History

Aminopyrine was introduced as an analgesic and antipyretic agent in 1897. Its general pharmacological properties are very similar to those of the salicylates, and it is an effective analgesic and antipyretic compound. Cardon et al [5] have cited the older literature concerning its effectiveness in a variety of conditions. During the 1920's it became very popular, and by 1930 it was widely used throughout the world. In the US it was reported that 30 million prescriptions per year were written.[6]

Some Commonly Prescribed Brands of Aminopyrine and Dipyrone

Aminopyrine	Dipyrone
Aminopyrine (Lilly)	Dipralon Forte (Arnar-Stone)
Amytal with aminopyrine (Lilly)	Fevanil (Carrtone)
Cibalgine (aminopyrine-allobarbital) (Ciba)	Key-Pyrone (Key)
Pyramidon (Winthrop)	Migesic (Misemer)
	Narone (Ulmer)
	Novaldin (Winthrop)
	Pydirone (Breon)
	Pyralgin (Savage)

Agranulocytosis, an often fatal disease characterized by an explosive onset of infection (usually a sore throat) and a virtual absence of granulocytes in the blood, was first described in 1922.[7] In the late 1920's, cases appeared in the US frequently, and in 1931 it was suggested that these were often related to the ingestion of drugs that were coal tar derivatives.[8] In 1933 Madison and Squier[9] established a causal relationship between aminopyrine and agranulocytosis by reproducing the syndrome with a test dose of the drug in patients who had previously developed the disease while receiving aminopyrine.[9] Kracke and Parker established this relationship beyond all doubt in 1935.[10] Of the 172 cases of agranulocytosis reported in the literature from September,

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In 1934, the Council on Drugs condemned the indiscriminate use of aminopyrine and criticized the confusing and uninformative names used for preparations containing the drug. As shown by the partial list in the Table, a comparable situation exists today with the derivative, dipyrone.

Pharmacology.—These two drugs are almost identical pharmacologically; sulfonation of aminopyrine to dipyrone renders it more soluble without affecting other properties. Both compounds are demethylated to 4-aminoantipyrine, a portion of which is then acetylated to 4-acetylaminoantipyrine. Neither of the parent compounds, antipyrine and 4-aminoantipyrine, has been used to any great extent systemically in this country and, although antipyrine is used topically, there have been no reports of agranulocytosis attributable to it. The structural formulae of these parent compounds are shown in Fig 3 and 4.

Efficacy.—Although it has been shown in animal studies that aminopyrine is an effective analgesic and antipyretic,[14,15] there are no reports of double-blind, randomized studies comparing either aminopyrine or dipyrone with any other drugs to determine their relative effectiveness. Nevertheless, there is little question of the efficacy of these two drugs as analgesics and antipyretics.[5] Wolff and associates studied the effect of a variety of analgesic drugs on the pain threshold in man. The effect of equal doses of aminopyrine and aspirin was identical.[16] For many years, however, the lack of use of either aminopyrine or dipyrone in this country has indicated that American physicians have obviously felt that they had no advantages over salicylates and similar drugs that would justify the danger attendant upon their use.

There have been only four articles in recent years in the American literature advocating the use of aminopyrine.[5,17-19] Of these, the report by Cardon et al presents the most persuasive argument for the occasional use of aminopyrine.[5] Aminopyrine afforded complete relief in six patients who had severe febrile illnesses in which the major symptomatology was referable to fever. Spear reported that of 74 patients with Hodgkin's disease whose charts he reviewed, 62 had fever.[17] He states that aspirin "given in a haphazard fashion" failed to relieve the fever in 31 of 35 patients but that in 18 of these patients aminopyrine, given every six hours, afforded effective relief. One can, of course, speculate on what might have been accomplished by the regular administration of aspirin or another relatively safe antipyretic. Another article recommends the use of aminopyrine for the treatment of diabetes insipidus, although it is not clear why the authors felt that the antidiuretic hormone was not acceptable therapy, since they had demonstrated its effectiveness in their patient as proof of the diagnosis.[18] The only other article advocating the use of aminopyrine presents no data.[19]

The unfortunate aspect of these articles is that the authors all minimize the incidence of agranulocytosis and state that the hazards of aminopyrine have been overemphasized. These statements have been refuted by Wintrobe [20] and by Trimble,[21] and it is appropriate to consider just how dangerous these drugs are.

Incidence of Agranulocytosis

Aminopyrine.—In a review article, Discombe cites the use of aminopyrine in four series of over 200 patients each, in which nearly all patients received the drug for at least 14 days and most for a much longer period.[3] The incidence of agranulocytosis ranged from 0% to 0.91%. The total number of patients in the four series was 1,272 and the total number of cases of agranulocytosis was 11, or 0.86%. Of the 11 patients who developed agranulocytosis, eight died (0.63%). Even if we add to these the 103 patients of Simon and Metz,[22] the 18 of Spear,[17] and the 6 of Cardon et al,[5] none of whom developed a blood dyscrasia, we will have a total of 11 cases and eight deaths in 1,399 patients, an incidence of 0.79% and a mortality rate of 0.57%. These are the only figures that a diligent search of the literature has revealed among patients who have received the drug regularly over a period of at least two weeks and who were observed during the period of administration.

Discombe [3] estimates that, in countries in which aminopyrine was freely available, there probably were two to five cases of agranulocytosis per 1 million inhabitants per year. It is very likely that in that era a large number of cases of acute sore throat secondary to agranulocytosis were not diagnosed as such and, even among those in whom the diagnosis was established, many cases may not have been reported. Dameshek and Colmes [6] estimated that there was one case of agranulocytosis for every 10,000 prescriptions of aminopyrine. This does not take into consideration the fact that the disease apparently requires a period of time for sensitization to occur, so that patients who received only a few doses would not be expected to have a reaction. Moreover, those who used the drug for a long period very likely had prescriptions refilled, so that 10,000 prescriptions may represent less than 10,000 patients.

Dipyrone.—Aminopyrine and dipyrone are so similar that there is no reason to suspect that they are not equally likely to produce agranulocytosis. The first case of agranulocytosis associated with dipyrone was reported in 1935.[1] Later, a human volunteer known to be sensitive to aminopyrine was given 0.65 gm of dipyrone, and he developed granulocytopenia eight hours later.[23]

The recent reports to the Registry on Adverse Reactions certainly indicate the potential of dipyrone for producing agranulocytosis; since 1955, 28 cases from the US and 9 from foreign countries

have been reported to the Registry. An additional 14 cases have appeared in the foreign literature. Of this total of 51 patients, 19 (37%) died.

Some of these case reports illustrate the cross-reactions between dipyrone and aminopyrine. One patient previously had agranulocytosis after receiving aminopyrine.[24] Of several patients who had recovered from dipyrone-related agranulocytosis, one developed full-blown agranulocytosis within 24 hours after being given 0.6 gm of aminopyrine; one reacted to a test dose of dipyrone itself [24]; and one was shown to have a positive skin test, serum leukocyte agglutinins, and positive response to a test dose with both dipyrone and aminopyrine. Three other patients were tested with dipyrone for the presence of leukocyte agglutinins, and the results in two were positive.[25-27]

Comment

This recent increase in the use of dipyrone and in cases of agranulocytosis and death resulting from it must give us pause, particularly since so many children are among the victims. We must consider whether there are any special advantages offered by these drugs that warrant the risk of a serious and possibly fatal reaction. From the articles urging the use of dipyrone, it is obvious that those who prescribe it are chiefly taking advantage of its antipyretic effect. However, there are several effective antipyretics on the market in addition to aspirin, and there are also physical measures that may be used to reduce acute pyrexia, particularly in children. The rather limited use of dipyrone and aminopyrine in this country in the past suggests that most physicians find these other drugs satisfactory, and there is a widespread belief that there are practically no circumstances in which aminopyrine or dipyrone is indicated.[4,28] Admittedly, reports indicate that some patients with fever respond well to aminopyrine after they fail to respond to aspirin,[5,17] but these would seem to be too rare to justify use before a thorough trial of other drugs.

The question facing the medical profession is whether the continued use of these drugs is justified. Seven deaths, three of them in children, have been attributed to dipyrone in the US in the past four years. Have this many lives been saved through use of the drug?

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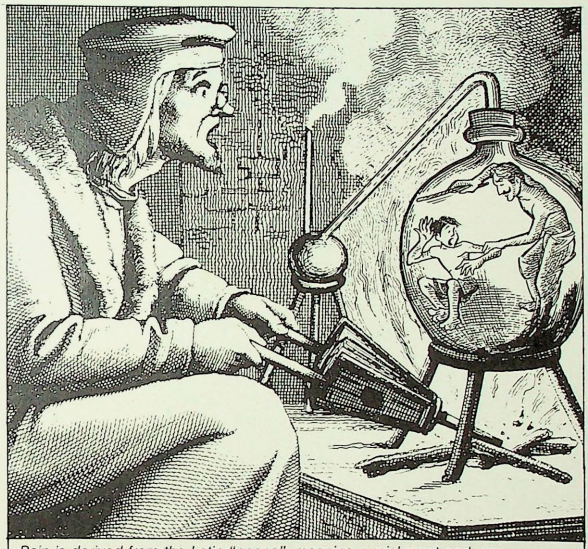
Editorial



Pain is derived from the Latin "poena", meaning punishment and was associated in early civilisation, with the concepts of demons, sin and punishment (Lasagna, Drugs 32, 4. p.2, 1986).

Pain and Fever, one or both these symptoms, account for the majority of presenting complaints to a physician. Viewed with a casual air, they are often vital clues to reach a diagnosis. Therefore, an update of the pathology and management of pain and fever is much called for.

Symptomatic treatment always vies with specific therapy. Yet its value in terms of relief obtained and improvement in well-being is the cornerstone of successful medicine. Patients expect to be rid of uncomfortable symptoms, even before the disease runs its natural course, thus promoting the physician to reach for the first analgesic and/or antipyretic agent. In satiating the demand for relief, there is sometimes a subtle suspicion of an accompanying risk.

However, running parallel to this demand for relief of unpleasant sensations is the concern that what can cure may also harm. Unfortunately emotional overtones cloud rational judgement. 'Weighing Risks', an article in this issue, suggests a rational approach to this problem. It examines the balance between risk and benefit with relation to not only drugs but also everyday events.

One result of the fear that has been induced by emotionally charged allegations of drug risks is the revival of fringe medicine — homeopathy, herbalism, hypnosis, acupuncture and iridiology. But alternate therapy or fringe medicine has yet to prove its worth under scientifically controlled clinical trials.[1] The recent report of the Board of the Science Working Party of the British Medical Association on Alternate therapy found no reason why it should not be assessed by the same scientific principles that are applied to conventional practice.[2]

The methods that were found to be useful are being investigated scientifically. These include acupuncture and hypnosis which are being currently featured. In some cases, alternate therapy can be dangerous as was demonstrated by the use of Laetrile.

On the other hand, the close control of pharmological and toxicological testing has reduced the chances of a drug being released for general use.[3] Great strides have been made in the field of adverse drug reporting and in statistical methods of evaluating risks. These have permitted a scientific approach to determine the true incidence rates of rare side effects. As an example, two studies designed to determine the incidence of rare adverse drug reactions, presented at the III World Conference of Clinical Pharmacology and Therapeutics held in Stockholm last year have been reported. These studies along with Weighing Risks have resulted in Weighing Risks — A Case in Point an article which demonstrates the need to cultivate a cautious and balanced attitude not only towards the 'victim oriented' press reporting but also to apparent 'scientific studies' which could be pivotal in decision making. A pertinent example relevant to this issue of the Medical Bulletin is the repeatedly quoted and outdated estimate of the risk of aminopyrine induced agranulocytosis by Discombe and Huguely — despite the fact that it was based on evaluation of data from different sources which are not comparable and which were arbitarily collected. [4] The results of these studies are in conflict with all practical experience[4] and have been disproved by the recent International Study on Agranulocytosis and Aplastic Anaemia reported in the October issue of the Journal of the American Medical Association.[5]

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Pain — A Review

As different as one person is to another, so is the experience of pain felt by each individual[1]; so, too, the resulting pattern of behaviour and reaction. Pain is a personal, private and subjective experience it is a hurt we feel; this underlies the affective element which is an integral part of the pain experience.

But different though each person may be to another, at another level they are alike; likewise pain has its commonly shared characteristics. It is these characteristics, — the emotionally neutral ones — that will be discussed here. The affective element is no less important but will be dealt with briefly. In many cases of chronic pain and, rarely, acute pain the affective element can drastically change the pain experience as in the famous and often cited example of soldiers on the battlefield who do not feel injuries when they occur[2]; or the less known one of walking barefoot over hot coals during neurolinguistic programming[3]. In these cases a strong emotion suppresses pain. On the other hand,a once brave and courageous person can be so affected by chronic pain to become a cranky, complaining, miserable and irrational creature.

Pain is considered a protective mechanism of the body which allows recognition at a conscious level that a harmful or potentially harmful stimulus or situation threatens the structural and functional integrity of the body — and if uncontrolled, subsequently of the mind too. It allows the person to respond to these threats with a battery of responses that will result in protection from,or avoidance of these stimuli. These responses range from a verbal 'ouch' to a conscious decision to visit a doctor and include postural adjustments, avoidance of movements, affective, autonomic and other physiological and neurological responses. A description of pain based on any one of these responses does not give a comprehensive view of the pain phenomenon, and stresses the need to take all the aspects of pain into consideration while determining treatment. To not do so can be detrimental to the patient: for example, a patient who has been diagnosed as having 'psychogenic pain' (on the erroneous belief that he has a painless pain) is treated exclusively by psychiatry.[1]

On the other hand,if it is decided that the pain is 'physical', one somatic treatment after another, each more desperate than the earlier, is prescribed.

Pain should be approached, considered and treated at all levels. This is all the more so in the cases of chronic pain as pain is a sensation which does not exhibit the phenomenon of adaptation and can therefore have many adverse effects on a patients life.

Pain can be conveniently viewed as acute or chronic; the difference being that in acute pain the sufferer can usually give a clear description of the location, severity, fluctuation, mode of onset and factors that aggravate or relieve it. This sort of pain usually responds well to analgesics. On the other hand, descriptions of chronic pain are comparatively vague and are influenced by cultural, religious and psychological factors; this pain does not respond as well to analgesics.

Furthermore,objective signs such as pallor, tachycardia, mydriasis, hypertension, sweating — (signs of autonomic nervous system hyperactivity) — are seen in acute pain and present a clinical picture of anxiety[4]. Chronic pain tends to cause disturbances in work, sleep, social, sexual and other functions and thus comes close to a clinical picture of depression[4]. The point at which acute pain — which serves the purpose of warning that something is wrong — becomes chronic varies,but is arbitrarily taken as six months.[5]

Pain is often experienced before other signs and symptoms of the disease occur. It is thus essential for the physician to understand well the sensory supply of the body surface and also the viscera as well as the differences in the quality and types of pain to reach a diagnosis. The sensory supply of the body surface is illustrated in Figure 1. A given spinal segment also supplies a visceral

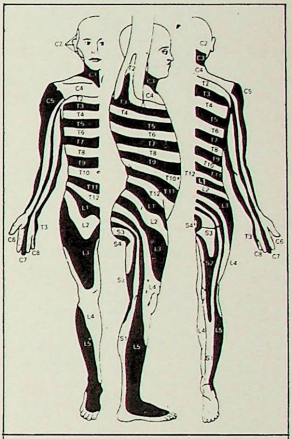

Fig 1: Sensory supply of body surface.

area with autonomic nerve fibres. The important nerves for intrathoracic viscera are the first to the fourth thoracic,while for the upper abdominal,the sixth to the eighth.

Superficial pain has two components — a quick pricking sensation, followed by a burning pain a few seconds later — this constitutes the double response of Lewis. Visceral and deep musculoskeletal pain have the quality of cramping or aching but can occasionally be sharp or burning. While superficial pain can be localized to a single sensory segment both deep musculoskeletal and visceral pain cannot be localized to closer than 2 to 3 segments and are often indistinguishable from each other; for example,the pain of renal colic may resemble that of a tear in the lumbar muscle in location and quality. Likewise,a tear in a muscle in the chest may resemble that of angina.

Due to a greater cerebral representation in the sensory supply of the integumen as opposed to that of the viscera, pain in the latter is often referred superficially. The location of the referred pain on the

Table: Dermatomes to which visceral pain is referred

Viscus	Spinal segments
Heart	C 3-5, T 1-8, usually on left occasionally bilateral
Lung	T 2-5
Oesophagus	T 5, occasionally T 6, 7, 8
Stomach	T 7,8,9 usually bilateral
Intestine	T 9-12, bilateral or on left
Diaphram	C 3-5
Liver	T 8-10 Right
Gall bladder	T 8-9, occasionally 5-7
Kidney	T 10, also T 11, 12, LI
Ureter	T 11, 12, L1
Testes	T 10
Epididymis	T 11, 12
Bladder	T 11, 12 L1, S3-4
Uterus & Ovary	T 10-12, LI, SI-4

surface of the body lies in the dermatome of the spinal segment which supplies the affected viscera. Table shows the sensory segments to which pain in certain viscera are reffered to. The paucity of pain representation in the viscera is eloquently described in the accompanying extract.

Harvey (1628, see 1962 ed.) remarked upon the absence of sensation in the exposed heart of Viscount Montgomery. Harvey records, "I carried the young man to the King (Charles I) that His Majesty might with his own eyes behold this wonderful case; that, in a man alive and well, he might, without detriment to the individual, observe the movement of the heart, and with his proper hand even touch the ventricles as they contracted. And His Most Excellent Majesty, as well as myself, acknowledged that the heart was without the sense of touch; for the youth never knew when we touched his heart ..."[7]

Occasionally an aberrant referral of pain occurs. Pain spreads to areas next to those that are affected. This happens due to pre-existing disease in adjacent areas which have already caused a partial depolarization in the neurones supplying these areas; which then easily become depolarized by the new disease[6]. A person with cervical arthritis might thus have the pain of myocardial infarction referred to the neck region.

Clinical Approach:

In dealing with a problem of pain a detailed history, general physical examination, neurological examination and perhaps a psychiatric evaluation are required. The importance of a detailed account from the patient on the history of the pain cannot be stressed adequately because it is on this information that the physician can arrive at a reasonable conclusion regarding the cause of the pain.

History:

The following inquiries should be made:

a) The location of the pain: This helps to identify the cord segment involved and will limit the diagnostic possibilities to be considered.

b) Exacerbating and Relieving factors: These pointers are valuable clues to the possible mechanisms producing pain. Pain on swallowing focuses attention to the oesophagus; back pain which worsens on sitting or walking suggests disc disease, while similar pain aggravated on lying down, suggests intraspinal disease.

c) Mode of onset: Pain reaching its 'full' intensity almost immediately indicates rupture of a tissue as in dissection of the aorta or in perforation of a peptic ulcer

d) Time of occurrence: Pain that occurs several hours after a meal and which is relieved by food suggests the action of acid on the stomach or duodenal mucosa. Joint pains that are more severe with the first movements after prolonged rest point to arthritis.

e) Quality of pain: A throbbing pain points to arterial pulsation as a cause. Sharp, stabbing and recurrent pains usually result from disease of nerve roots or sensory ganglion. What is important is to determine whether the pain is steady or fluctuating. A steady pain is found in peptic ulcer, angina pectoris, gall-bladder colic and renal colic. With the latter two, the word colic is misleading as the pain is actually steady[6]. True colicky pain suggests the obstruction of a hollow viscus[6].

f) Duration: Anginal pain rarely lasts more than 15 minutes; in contrast the pain of myocardial infarction persists longer.

g) Severity: Determining the severity of pain based on the persons judgement is difficult as people differ in their tolerance to pain. Pain should be taken to be severe if it interferes with the person's work, sleep or social activities, is accompanied by physiological signs or requires therapeutic intervention.

After a systematic interrogation, measures which reproduce and relieve pain should be attempted,as these, apart from confirming the pain mechanism, convince the patient that the doctor understands his problem.

A psychiatric evaluation along with the inquiry regarding pain should be done and signs and symptoms of depression,such as loss of sleep and appetite, loss of weight, reduction in social pain and sexual functions should be noted especially in chronic pain.

General Physical Examination:

Begin with the site of pain. Examine the area for any swelling, deformity and redness. Palpate for tenderness, check if temperature of area is raised.

Joints should be taken through the full range of movement,noting if the character of the pain changes.

Nerve trunks should be palpated and stretched. A neurological examination should be performed. If there are any neurological abnormalities, one can assume that the pain is due to it,but one cannot rule out the involvement of the nervous system in the absence of such abnormalities.

Laboratory tests and other

investigations are determined and depend entirely on the possible cause of the pain.

Management:
An important consideration in pain management is the possibility that the cause of pain can be eliminated. Even if one cannot eliminate the cause, it is possible to reduce pain more easily if one is aware of the origins of the discomfort.

Before considering the management of pain, the pathway of the pain sensation and the sites of drug action should be clearly understood. Figure 2 illustrates this in brief. Though the main site of action of the non-narcotic drugs is by the inhibition of prostaglandins at the periphery, some, like analgin, also have a potent central nervous system effect.

Paracetamol also possesses a CNS effect, but its mode of action is unclear[6] as it has a weak effect on prostaglandin synthesis.

The side-effects of the non-narcotic analgesics are also related to their inhibition of prostaglandin synthesis; the most common being the ability to induce gastric or intestinal bleeding and ulceration[7]. Other side-effects include renal toxicity, hepatotoxicity and allergic reactions. In cases of hepatic disease or overdose of the drug, paracetamol is potentially fatal. Though rare, aspirin usage has been significantly linked with the fatal Reye's Syndrome in children with concurrent viral infections and should therefore be avoided in children. The use of this drug is now banned in India for children under 12 years of age.

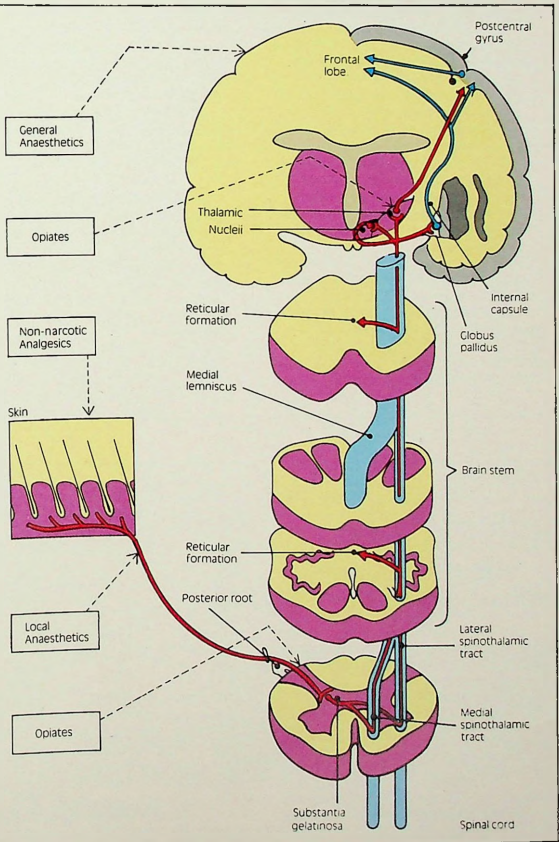

Fig.2 : Pain pathway and sites of action of drugs

Though these drugs are classified as effective in pain of low to moderate intensity, this is not altogether true. In cases of post-operative pain, non-narcotic drugs are preferred to narcotic analgesics.

What is, however, notable about the long list of non-narcotic drugs is not so much the difference between them but the striking similarities in drug action. Some of these drugs such as aspirin and analgin also possess anti-inflammatory and antipyretic actions. Rather than attempt to memorize the long list of drugs and their minor differences, the physician should familiarise himself with a few preparations.

The weak narcotic analgesics may be used for mild to moderate pain, but as there is a slight euphorant effect, they should not be used for long periods of time as they carry the potential for addiction. In these cases the patient's mental status should be well assessed.

The potent narcotics have their use in severe visceral pain, severe pain due to trauma including post operative care and the pain of advanced malignant disease.

Mention must be made here of the recently recognised neurotransmitters, encephalins and endorphins, in pain relief. These endogenous peptides have a profound and long-lasting analgesic effect and have been found in various parts of the nervous system, namely, the periaqueductal gray matter, medullary raphe, the neurons in the dorsal horn of the spinal cord, in the thalamus and the frontotemporal cortex. Their action is blocked by the opiate antagonist naloxone and they are therefore part of a natural endogenous analgesic system. They also probably play a role in the analgesic response to opiates.

Another major inhibitory pathway in the pons appears to inhibit the nociceptive responses of the dorsal horn neurons.

Guidelines:

The management of pain should observe the following guidelines.

a) Identification of the cause — Certain conditions can be treated by particular agents, for example, the pain of angina pectoris responds to glyceral trinitrate; trigeminal neuralgia and the lightning pains of tabes dorsalis to carbamezepine. Bone pain from metastatic prostate cancer responds to stilbestrol and post herpetic neuralgia to carbamazepine along with a tricyclic antidepresant.

b) Begin with the simplest method (or drug) but with early treatment and adequate dosing. There is strong evidence that if pain is not treated for an extended period of time, abnormal excitatory states arise in the CNS so that treatment which would have earlier relieved the pain does so no longer.

   Oral drugs are preferable to parenteral drugs as they are drugs with few side-effects and low addictive liability.

c) For the same reason, adequate timing between doses and adequate dosing is essential; especially in chronic pain which should be considered a serious problem and treated so that the patient is made as comfortable as possible. Drugs and doses should therefore be tailored to the needs of the individual.

d) More than one kind of treatment should be utilized. This could be drug combinations, adjuvant analgesics, other drugs or physical methods. Non—pharmaceutical methods of pain control such as acupuncture, hypnosis, biofeedback, relaxation techniques and coping skills should also be tried. Adjuvant drug therapy mentioned above includes psychotropic drugs which are sometimes useful in chronic pain since they alleviate the associated depression and improve the quality of life. Benzodiazepines are useful if anxiety plays a part; chloral hydrate, if insomnia is present; antiemetics counter the nausea and vomiting associated with short-term treatment with morphine, and laxatives reverse the constipation associated with the long-term use of narcotic analgesics.

Each case must receive a full trial of analgesic drugs and other concommitant physical methods to relieve the pain. Destructive methods such as rhizotomy or cardotomy should be tried as a last resort especially since these procedures yield only temporary relief; in some cases the pain that recurs is worse than it was prior to the operation.

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Psychological Aspects of Pain

Psychological factors can influence pain behaviour — to varying extents — in a considerable number of patients. The importance of this lies in its effect on the management of persons suffering from pain; patients then need not undergo expensive and lengthy investigations and, also the development of many psychological techniques based on this, offers help even to those suffering from pain due to somatic reasons.

Both physiological and psychological factors are responsible for the existence. perception and persistence of pain. At one pole are patients with pain that is completely psychologically determined; at the the other end are patients where pain is physically determined; inbetween lie patients where an interplay between somatic and psychogenic factors exists — here the character and experience of pain is not fully accounted for by the lesion.

In the psychological disorders that are associated with pain, such as conversion hysteria, depression, anxiety and schizophrenia, it is only when the underlying disorder is corrected that the patient experiences relief.

Symptoms of an underlying psychiatric disorder may be discovered by careful questioning. The commonest psychiatric disorder associated with pain is conversion hysteria; the patient presents with dramatic complaints, yet may show indifference to the symptoms, for example. the patient may smile while talking about his pain. Patients with this disorder often have a history of previous episodes with remissions and relapses.

Depression is another frequent cause of pain; the patient gives a history of feeling depressed before the onset of pain. Questioning may reveal that things which had previously given him pleasure were no longer so. In addition, physiological parameters of depression, such as loss of appetite, decrease in sleep and loss of sexual desire may be noted. On the other hand. patients with organic illness often become depressed as a result of the pain, moreso in cases of chronic pain. The schizophrenic patient is likely to have bizarre complaints with disturbances of thought and behaviour.

Once a diagnosis is made, the physician has a large therapeutic armamentarium to draw upon; placebo, biofeedback, hypnosis, behaviour modification, psychopharmaceutical agents and psychotherapy to name a few. A psychiatric disorder like schizophrenia responds to antipsychotic drugs and psychotherapy, as does depression to antidepressants. It is important to remember that a depressed person is likely to improve with antidepressants even if the depression is secondary to pain due to an organic lesion.

Many patients respond to placebo, but this does not necessarily mean that the pain is psychogenic. What it does mean is that the patient is a placebo responder and that he/she may yet have an organic lesion.

Probably the most powerful tool in acute or chronic pain, organic or psychologically caused, is hypnosis· in this state the person can distort his/her perception of the pain to warmth or pressure, thereby preserving the signal functions of the pain. Hypnosis can also be used to induce analgesia or anaesthesia. The advantage of hypnosis lies in the absence of demonstrable physiological risks. An example of its usefulness was demonstrated by Dr. James Esdale, a Scotish surgeon in Calcutta who. in the pre-anaesthetic days of the 1850s performed 500 major and 1500 minor surgical operations under hypnosis. He often undertook operations that in his day were considered too dangerous to contemplate.

Behaviour modification has also been found very useful in pain management. Pain is often reinforced by rest, medication and attention focused on the patient by medical personnel and family members. In this approach, patients are reinforced for behaviour not compatible with pain: rest and attention from others is made contingent on increasing activity levels and decreasing complaints of pain. Analgesics are given by the clock and not when the patient complains of pain.

Biofeedback is yet another powerful modality and has been found useful for muscle tension headaches (electromyography feedback) and migrane (skin temperature biofeedback) with as many as 70 per cent of patients remaining free of migrane one year after treatment. In addition to these methods are many other psychological ones; psychotherapy, where the patient is challenged to get well and to specify realistic relationship, work and recreational goals and the patient is reinforced for objective evidence of attempts to achieve the goals set.

Dr. J.D. Mirchandani, MD, DPM, FIPS, Bombay

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"It is important not to forget that non-drug approaches often have a great deal to offer to the patient with pain and that a multidisciplinary approach is often preferable to a solely pharmacological one."

"Consider the common experience, for instance, of being able to relieve quickly, by means of a hug and reassurance, the distress and suffering of a child who had tripped and fallen."

"In moments of excitement, stress or competition, such as on the athletic field significant injury can be unattended by pain."

"Reassuring patients prior to surgery can have a beneficial effect on the course of post-operative pain and requirements of analgesics."

Louis Lasagna — DRUGS, 32 (4), 1-7, 1986.

Facts on Fever

Fever is one of the commonest presenting symptoms a general practitioner encounters, but it serves merely as an indicator — a sensitive, objective and reliable one — of a disturbance within the body except in a few instances. It should not be unnecessarily viewed with alarm and panic.

These few exceptions are pyrexia of moderate elevation in patients with central nervous system disease, decreased cardiovascular function (the increased oxygen demand, cardiac output and pulse rate associated with fever can be dangerous on the already compromised myocardium in these cases); a history of previous febrile seizures (particular in children) and in pregnant women (fever may be teratogenic for the developing foetus).[1] A potentially fatal example is heat stroke, where temperatures greater than 106°F (41.1°C) are common. Heat stroke is classified as a hyperthermia syndrome; these are cases where the hypothalamic thermostat remains at the normothermic level, unlike cases of 'fever' where the setting is at a higher level. In hyperthermia the heat loss mechanisms fail, causing temperatures that in some cases have been recorded as high as 112-113°F (44.4°C)[2]. Temperatures higher than this are probably incompatible with life; in fact, irreversible brain damage is common at temperatures of 108°F (42.2°C) and convulsions are common at 106°F (41.1°C)[3]. Usually hyperthermia is seen with cerebral lesions that involve the hypothalamus[2]. Another condition that causes dangerously high temperatures is malignant hyperthermia; this is a group of inherited disorders which results in temperatures of 102.2°F to 107.6°F in response to certain inhalational anaesthetic agents, such as haloperidol, cyclopropane, ethyl, ether or muscle relaxants, especially succinylcholine[2].As with other causes of hyperthermia, this should be considered an emergency and treated immediately. The most effective measures in hyperthermia are ice-water baths and, depending on the cause, other measures, such as dantrolene sodium, which is specific for malignant hyperthermia, paying special attention to hydration, electrolyte and acid balance.

Teas or infusions made up of herbs like sage are a common household remedy for fever.

What is generally termed as 'fever' is an elevation of the normal body temperature which, depending on the individual, varies between 97-99°F (36.1-37.2°C). This includes the diurnal variation of 1°F (0.6°C). It is safe to consider an oral temperature of above 99°F (37.2°C) as an indicator of disease. (Rectal temperature is usually 0.5 to 1°F higher than oral temperature).

The following disease states are accompanied by fever:

1. All infections, whatever be the offending micro-organism. The majority of febrile illnesses of less than 2 weeks duration can be attributed to this.

2. Tissue damage due to any cause. Vascular accidents such as myocardial or cerebral infarction or mechanical injury frequently cause fever.
3. Neoplastic diseases. Hodgkin's and other tumours of the reticuloendothelial system can present with fever. The production of EP/IL-I is thought to be responsible. Solid tumours can cause fever which is probably due to obstruction or infection consequent to the tumours.
4. Drug fever and other conditions that involve the immune mechanism, such as connective tissue diseases.
5. Metabolic disorders, such as gout, porphyria, Addisonian or thyroid cases, are occasionally responsible.

Pathogenesis Of Fever

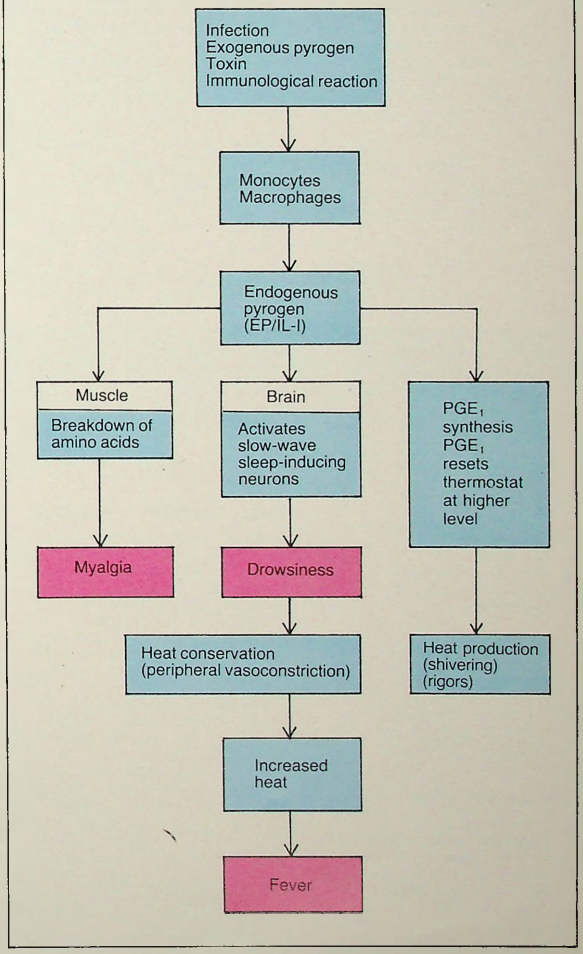
The temperature of the body is regulated almost entirely by nervous feedback mechanisms and most of these operate through temperature-regulating centres in the hypothalamus. The principal area of temperature regulation lies in the preoptic area and, also, to some of the adjacent parts of the anterior hypothalamus. These areas contain heat-sensitive neurons which increase their firing rate in the presence of endogenous pyrogen.

Fever is best understood using the analogy of a thermostat. The regulatory system at the hypothalamus balances heat production and heat loss. Heat production is principally promoted by increased shivering and by peripheral vasoconstriction which reduces heat loss. Heat loss occurs by vasodilation (full vasodilation can increase the rate of heat transfer to the skin eight-fold and by sweating (1°C) increase in body temperature can cause enough sweating to remove ten times the basal rate of heat production).[4]

In fever, the thermostat is at a setting higher than normal which causes signals to increase heat production. The tone in the muscles consequently increases which results in shivering, which commonly occurs during a fever. Conversely, when fever comes down, the uncomfortable flushing and sweating is due to the loss of body heat in accordance with the temperature 'reset' at the hypothalamus.

Fever is caused by many stimuli which include bacteria, their endotoxins, viruses and other micro-organisms, hormonal substances, immune reactions and drugs; these are termed exogenous pyrogens and cause the release of endogenous pyrogen which is a product of macrophages and monocytes. Endogenous pyrogen has now been identified as interleukin 1 (IL-I) and it is believed to be the basis for many of the reactions under the umbrella of the 'acute phase response'.[2]

Genesis of fever



IL-I is responsible for setting the hypothalamic thermo-regulatory system at a higher level. The mediators responsible are prostaglandins of the E series whose synthesis is induced by (IL-I). PGE activates the heat – generating and conserving mechanisms by inducing the synthesis of cyclic adenyl monophosphate.[2]

EP/IL-I is probably responsible for other symptoms that occur during fever. It mobilises amino acids from muscles through a mechanism mediated by PGE; these amino acids act as nutrients for other cells. The myalgias experienced during fever and the muscle wasting that occurs in febrile states is therefore a result of EP/IL-I production.[2]

EP/IL-I also activates slow-wave sleep-inducing neurons which explains the drowsiness and prolonged sleep characteristic of febrile illnesses.[2]

On the positive side, EP/IL-I plays a key role in activating immune responses, in mobilising T. helper cells from marrow storage pools, in inducing lysosomal discharge in neutrophils, and in generating chemotactic activity in neutrophils.[2] It also activates fibroblasts to synthesize collagen and presumably contributes to tissue reparative responses.[2]

Manifestations of Fever

Subjective Symptoms

a) Sensations of feeling cold or warm chills
b) Headache
c) Myalgia, arthralgia
d) General malaise
e) Drowsiness

Objective Signs

a) Elevated temperature
b) Increased respiratory rate
c) Wide pulse pressure
d) Rapid pulse rate (except in typhoid fever and certain hypothalamic tumours)
e) Delirium

Laboratory Findings

a) Elevated ESR
b) Increased neutrophil count
c) Decreased serum iron and zinc levels
d) Concentrated urine with high specific gravity.

Management

Given the complexity of responses that occur during fever, controversy often surrounds its treatment. Specific therapy should, of course, be initiated. Antipyretic drugs, such as aspirin,analgin or paracetamol, should be employed, particularly when fever poses a high risk, such as in patients with a history of seizures (especially children), with heart failure, head injury, mental disorders or pregnancy.

Antipyretics are sometimes associated with unpleasant sensations due to the sudden lowering of body temperature. This is mitigated by a liberal fluid intake and administering the prescribed antipyretic drugs frequently and regularly.

If rigors are severe, an intravenous injection of calcium or morphine sulphate or chlorpromazine is helpful.

Physical methods, such as tepid water sponging, can also be initiated.

Of the common antipyretics, aspirin should not be used in patients with a history of salicylate sensitivity, or with a history of erosive pathologies, gastric ulcer patients with haemophilia and other diseases of blood coagulation and even asthma. It should also not be used in children due to the potentially fatal Reye's Syndrome. It is on this account that aspirin has, in U.K. and recently in India, been banned for children below the age of 12 years.

Fever of Unknown Origin (FUO)

Perhaps one of the most challenging problems in general practice is FUO. Though the problem may ultimately become obvious, its elucidation requires a detailed and careful history, thorough physical examination, appropriate laboratory examinations and occasionally even imaging techniques.

The term FUO should only be applied to those cases where the duration of fever exceeds 3 weeks and where intensive study of the case for at least a week fails to reveal the cause.[6] Some conditions that present in such a manner are given below:

a) Infections —
   i) Tuberculosis and atypical mycobacterial infections, especially if extra-pulmonary and involving the bone, lymph nodes, genital or urinary organs or peritoneum.
   (Other granulomatous infections that should be kept in mind include actinomycosis, candidiasis, histoplasmosis).
   ii) Bacterial endocarditis.
   iii) Bacteraemia due to Salmonella, Neisseria and Brucella.
   iv) Abscesses are a common cause and often arise in the abdomen and pelvis. Amoebic abscess or hepatitis should be ruled out.
   v) Urinary and biliary tract infections.
   vi) Viral infections caused by Epstein Barr or cytomegalo virus are becoming more common in immunocompromised hosts.
b) Neoplasms — A number of neuplasias are associated with fever; at least 20 per cent of FUO will have an underlying tumour as a cause and the percentage of such patients is increasing.[1] These neoplasms include Hodgkin's (in this case fever may be a principal symptom) and other lymphomas, leukaemias, solid tumours and a trial myxoma.
c) Granulomatous diseases — Sarcoidosis, if in an extra-pulmonary site, often presents with fever. Fever is also a prominent feature in regional enteritis. Granulomatous hepatitis of unknown aetiology is also a cause of FUO.
d) Inherited disease — The commonest of the inherited diseases presenting as FUO is Familial Mediterranean Fever (FMF), which is common in Armenians, Sephardic Jews and Arabs. Inherited hyperlipidaemia (Type 1) can also present as FUO, whereas it is a prominent sign in Fabry's disease.
e) Drug Fever — Allergy to antibiotics especially penicillin and sulphonamide may be a cause for prolonged fever and can compound diagnosis. Other drugs causing fever include bromides, iodides, arsenicals, procanimide, thiouracil, hydrallazine, phenytoin, barbiturates, quinidine and laxatives.[6]
f) Factitious Fever — There is a small group of patients — generally young women with FUO — who complain of fever or contrive to cause the thermometer to register high temperatures.

These patients are found to have psychiatric problems.

Management

As it is assumed that patients are categorized as having FUO after all routine tests (Table) have been carried out, the next question relates to determining the cause of the elevated temperature.

Table: Routine Tests

1. Total blood count
2. Blood culture
3. Urinalysis/urine culture
4. Blood chemistry
5. Chest x-ray
6. Stool examination

The causes are many, so it is essential that the physicians re-evaluate the patient thoroughly. Questions covering contact with animals, place of residence and recent travel, illnesses, drug intake and localizing signs may provide a lead to the affected organ system or possible infectious agent.

Physical examination should be repeated. Skin and mucosal lesions must be searched for; lymph nodes must be palpated with special attention to supraclavicular and axillary areas; careful palpation of the abdomen, rectal and vaginal examination should be done; valvular anomalies should also be searched for. Drug intake should be curtailed for 48 to 72 hours.

Laboratory tests

There are no specific guidelines to follow: tests should be aimed at the most likely system that could be affected, for example, if there is a suspicion of a connective tissue disorder, tests as to detect rheumatoid factor, antinuclear antibody and antistreptolysin titre may provide a clue.

Special attention should be paid to the abdomen, as many of the causes of unexplained pyrexia lie within.

Treatment

This depends entirely on the diagnosis which should be possible in 90% of patients with FUO.[5] Fortunately, of the remaining, the majority recover spontaneously or respond to medical or surgical treatment.

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4. *Textbook of Medical Physiology, Ed: Guyton AC, Igaku Shoin/Saunders, 7th Ed, 1986, 849-60*
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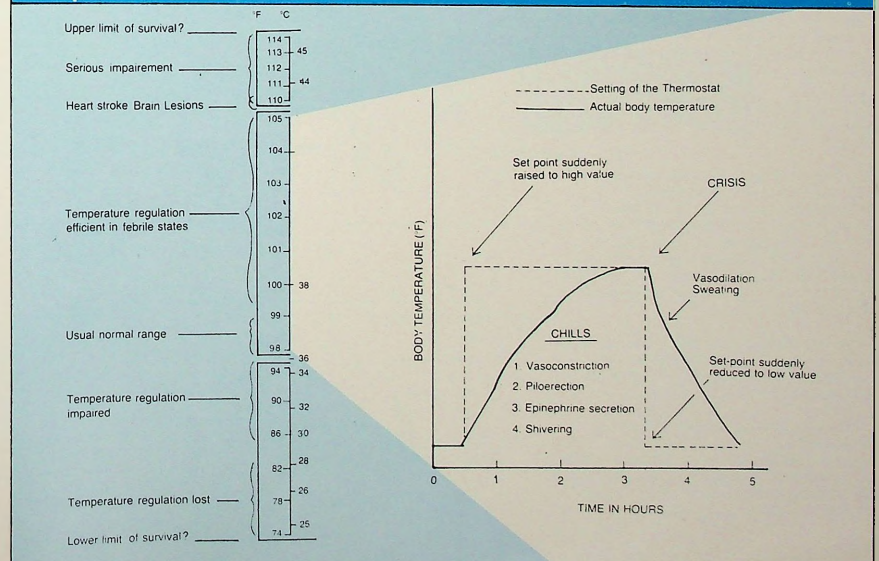
Body temperatures under different conditions and effects of temperature change on the "hypothalamic – thermostat".



Adapted from: Textbook of Medical Physiology Guyton AC: 7th Ed. W.B. Saunders Co.-Igaku-Shoin Saunders, U.S.A., 1986 p.849-860

The International Study on Agranulocytosis and Aplastic Anaemia (ISAAA)

Agranulocytosis and aplastic anaemia are exceedingly rare blood dyscrasias which have been loosely associated with several drugs. Both disorders can be caused by many environmental, biological and chemical factors, including over 100 pharmaceutical drugs. Many of these drugs have been implicated solely on the basis of case reports, or without controls, or on incomplete data reports.

Intentional rechallenge is ethically unacceptable and specific laboratory tests do not exist either to label the cause-effect relation. Therefore, to obtain a reliable estimate of the incidence of the risk of agranulocytosis and aplastic anaemia, the only reasonable approach medically acceptable was to undertake a rigid case-control epidemiological study.

This was the genesis of the International Study for Agranulocytosis and Aplastic Anaemia.

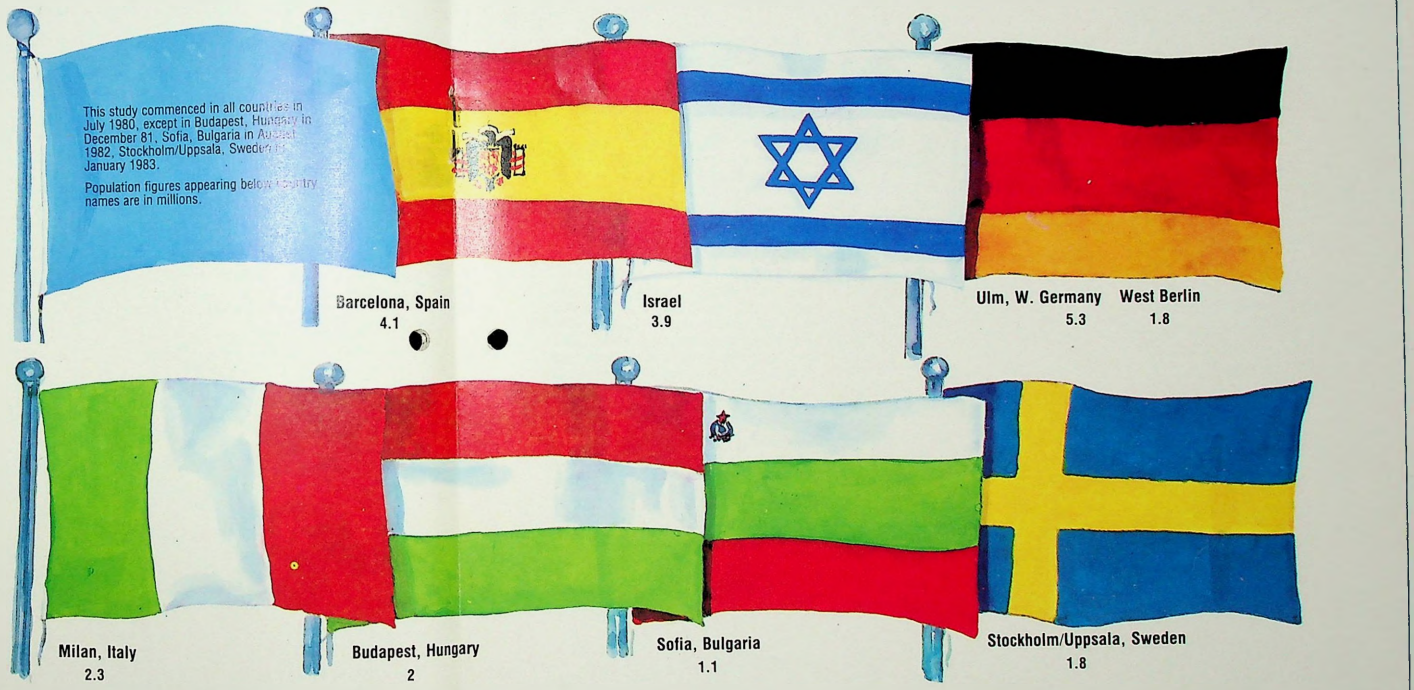
The study had a supervisory International Honorary Advisory Board to guarantee full independence between the organisers and the sponsors. This Board comprised eminent experts in medicine and haematology whose members were Sir Richard Doll (Oxford), Chairman, P.K. Lunde (Oslo) and Soen Moeschlin (Sweden).

All co-ordination and data analysis was done at the Drug Epidemiology Unit at Boston.

Carefully defined cases, diagnosed and reconfirmed by an independent haematological review committee, were searched for in a time-span of four years. For each diagnosed case, at least 4 controls were selected who could match totally with the cases based on age, sex, occupation, education, social status and such features.

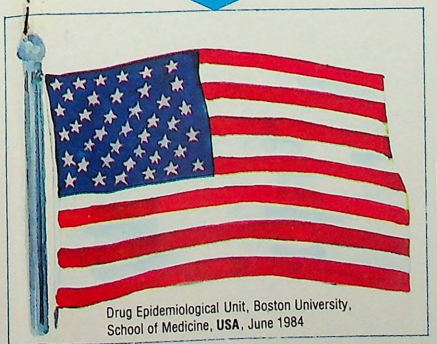
Specially trained staff questioned all cases and controls. All haematological data diagnosis was in line with international diagnostic criteria.

The study covered 300 hospitals in 6 countries, i.e., Israel, W. Germany, Hungary, Italy, Spain and Budapest, with more than 40 investigators specially trained to determine drug exposure and other related risk and disease factors.



Aplastic Anaemia

Cases 113	: Controls 1724
General Incidence	: 2.2 per million per year
Drug Associations Drugs	: Excessive risk per million in 5 months period*
Indomethacin	: 10.1
Diclofenac sodium	: 6.8+
Butazones (phenylbutazone, oxyphenbutazone)	: 6.6+
Fatality rate	: 49%



Agranulocytosis

Cases 221	: Controls 1425
General Incidence	: 6.2 per million per year
Drug Associations Drug	: Excessive risk per million in 1 week*
Dipyrone	: 0-1.1**
Indomethacin	: 0.6
Butazones	: 0.2
Salicylate	: Borderline significance
Thyrostatics	: 5.9
Sulfas	: 1-3
Fatality rate	: 9%

* Drug-induced agranulocytosis is characterised by short induction period unlike aplastic anaemia where considerable delay occurs between exposure and diagnosis ** due to regional variability + Risk proportionately higher if taken regularly and for sustained periods

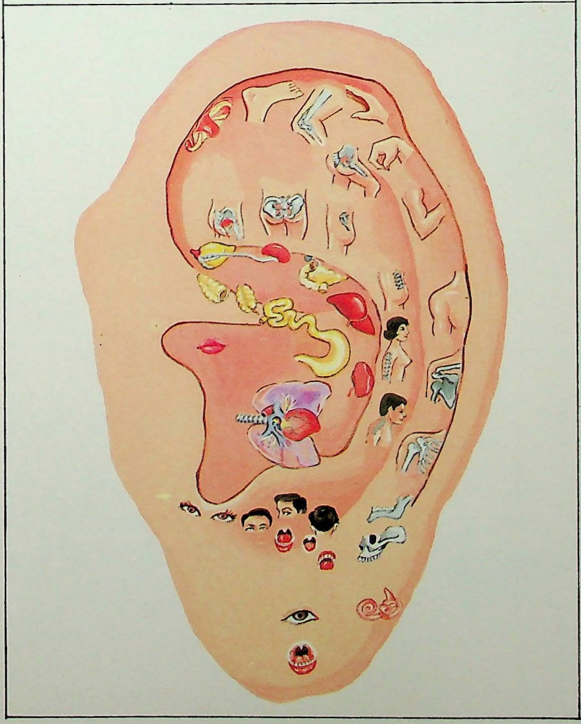
Acupuncture in the Treatment of Pain

The late Dr Albert Schweitzer once said, "Pain is a more terrible Lord of Mankind than even Death Himself." The truth of this saying is apparent to all, yet forgotten when we are not affected with the symptom. Most physicians pay inadequate attention to the treatment of this symptom as it is a purely subjective phenomenon which is difficult to assess objectively in clinical practice. Different patients have different pain thresholds and hence respond differently to similar ailments.

Western medicine is able to deal adequately with acute severe pain using narcotics which are however unsuitable for prolonged use in chronic pain due to their potential for habituation and addiction. And the range of analgesics available — including the new range of non-steroidal anti-inflammatory drugs — are occasionally inadequate to treat chronic pain.

Acupuncture offers an effective alternative to the problem of pain, both in its acute and chronic form. At present enough evidence exists of its ability to relieve pain and to create analgesia profound enough to carry out surgery ranging from Caesareans to Craniotomies and open heart surgery. We are as yet unable to define exactly how acupuncture produces analgesia, and several theories have been propounded to explain the mechanism of its action. As none of these is able to completely explain its action, it is probable that acupuncture produces analgesia at multiple levels and the true mechanism is a synthesis of the theories described below.

Auricular points in acupuncture



The 'gate control' theory of Melzack and Wall propounded in 1965 is the most popular neurological theory for the mechanism of action of acupuncture in the treatment of pain. According to this theory, perception of pain is modulated by functional gates within the central nervous system. Under normal circumstances, this gate is wide open and pain impulses which are carried by the small diameter fibres get through quite easily. When acupuncture needling is carried out, a second stream of non-painful impulses is set up via the large diameter fibres which cause overcrowding or jamming at the gate, causing it to close. There is, therefore, a competitive inhibition of the pain impulse at the gate. This gate is postulated to exist at the thalamic level.

The action of acupuncture should then be mediated through the large diameter fibres. However, it was seen that trans-section of the large diameter fibres diminished but did not abolish the analgesic effect. This led to the finding that the autonomic nerve fibres accompanying the blood vessels were also stimulated by acupuncture. The development of the humoral theory of the action of acupuncture was the result of this, as it was seen that acupuncture released morphine-like analgesic substances both in the brain and peripheral tissues. Over a hundred neurotransmitters have been isolated which play a role in acupuncture analgesia. The two major groups of these are the endorphins and encephalins which are produced by the lysis of beta-lipotropin.

Pomeranz suggested that the endorphins and encephalins produced by a neuron,binds to an opiate receptor on the terminal of an excitatory neuron,partially depolarizing the terminal membrane, thus reducing the net depolarization produced by arrival of a nerve impulse.

Stimulation of different acupuncture points augments the secretion of different analgesic substance and produces analgesia in different areas. Stimulation of the acupuncture point HEGU situated on the dorsum of the hand between the 1st and 2nd metacarpal bones leads to production of alpha-and beta-endorphins in the ratio of 2:1. Alpha-endorphins induce analgesia in the region of the head and cause a slight tranquillisation. Hence,this point is used to treat toothaches, headaches, and trigeminal neuralgia, as well as to create analgesia for tooth extraction and tonsillectomy. Beta-endorphin creates analgesia all over the body and is released by stimulation of most acupuncture points. These substances also cause slight sedation which potentiates the analgesic effect.

Acupuncture, contrary to popular belief, is not very painful. Acupuncture needles are normally 30 to 36 gauge (0.32 mm to 0.18 mm in diameter), which is little thicker than a human hair. The photograph shows a little girl undergoing acupuncture therapy.

In osteoarthritis, damage to the articular surface causes pain. This leads to a protective spasm of the surrounding muscles to restrict movement and pain.

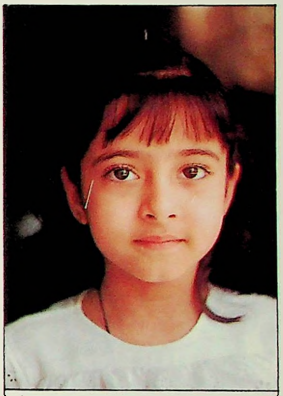
This spasm also pulls the joint surfaces closer and increases damage to the articular surface. This again creates pain, setting up a *vicious cycle (see Fig below).*

This cycle is difficult to break with conventional medical treatment. Acupuncture relieves the pain in sittings,thus breaking the cycle and affording the patient a pain-free existence for 2 to 5 years before the pain recurs.

In sciatica, we needle points which lie along the course of the sciatic nerve. This serves to relieve the pain and relax the muscular spasm of the paraspinal muscles, making movement easier. This is effective in giving relief from pain within 8 to 10 sittings in most patients.

Acupuncture is also effective in relieving pain by needling areas which are distant from the affected area. In frozen shoulder, a needle placed a few inches below the knee next to the tibia and rotated vigorously for a minute permits immediate pain-free mobilisation of the shoulder. This is one of the most dramatic demonstrations of the efficacy of acupuncture.
Acupuncture points are situated on a series of pathways called meridians which criss-cross the body. These pathways are traditionally said to allow the flow of certain life forces. Needling is said to restore the balance of these forces,the disruption of which was thought to cause disease.

Similarly, there exist acupuncture points in the ear (over a hundred of them) by the use of which it is possible to treat most ailments. The entire human body is represented in the ear in the form of an inverted human foetus. The facial area is represented in the lobule of the ear and the feet near the apex of the ear. This can be used to treat a wide variety of ailments like headache, hypertension, insomnia, gastritis, sprains, sciatica, dysmenorrhoea and pain anywhere in the body.



A young patient undergoing acupuncture therapy.

Acupuncture is a complete system of medicine and, like all systems of medicine, has a treatment for most conditions.

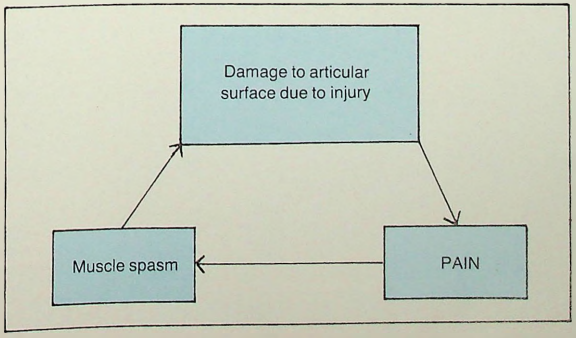
The use of acupuncture needles can be substituted in many cases by stimulation with lasers. This is as effective as acupuncture and is extensively used for treatment in children and thin individuals.

Electro-acupuncture, cryoacupuncture, and acupuncture using ultrasound, are other methods which are used to stimulate acupuncture points.

Acupuncture, the 5000-year old Chinese system of medicine,is an effective method for treatment of pain both in its acute and chronic forms. In skilled hands, it yields results which border on the miraculous. To quote Dryden, in conclusion, is apt:

"For all the happiness mankind can gain
Is not in pleasure, but in rest from pain."

Dr. Manik Hiranandani, M.B., B.S., D.Ac, M.D. F.F. Hom



Weighing Risks

Taking risks or avoiding them is intrinsic to life. As we grow older we veer away from the former towards the latter with the quest for vanished youth during the middle years expressed by a shiftback, for a short time, towards risk-taking again.

To grasp opportunity, one must act, and inherent in this,is the element of risk; opportunity and risk cannot be separated. When fear paralyses action, opportunity fades.

Understanding risk means learning to balance fear and opportunity. In this attempt strange paradoxes occur which highlight the magnitude in which risk is misunderstood, and this is the basis for some of the strikingly distorted perceptions of risk!

Cigarette-smoking is deemed responsible for half-a-million premature deaths per year from lung cancer and heart disease in the U.S. alone — but this fact only gets a small amount of coverage in the news media even though the number of smoking-related deaths is equivalent to three fully loaded 747 jets crashing every day. Yet, when an actual jet crash occurs, it is given "Big Attention".

That 'bad news' sells is nothing new. What is new is the instantaneous dissemination of news — one of the gifts of modern electronic technology.

Many widely accepted human activities are the very essence of risking life or limb. (Table)

Quantifying or measuring risk permits a rational approach which can allow people to make their choices based on information rather than on imagination. Information is crucial to this concept, but the methods of generating the information that one needs to assess risk are often uncertain and, moreover, the methods of communicating this information, viz., expressing risk are usually confusing, misleading and emotionally charged.

To understanding risk, one has to take a big step beyond the journalistic view. It is necessary to perceive the number of victims in relation to the number of people who did just what those victims were doing,but yet managed to emerge unharmed. This would be the genesis of avoiding what is known as ***Victim-Oriented Reporting.***

Table: Risks estimated to increase chance of death in any year by 0.000001 (1 part in a million)

Activity	Cause of death
Smoking 1.4 cigarettes	Cancer, heart disease
Drinking 0.5 litres of wine	Cirrhosis of the liver
Living in New York for 2 days	Air Pollution
Travelling 150 miles by car	Accident
Flying 1000 miles by jet	Accident
Living in average stone or brick building for 2 months	Cancer due to natural radioactivity
1 chest x-ray taken in a good hospital	Cancer caused by radiation
Living with a cigarette smoker for 2 months	Cancer, heart disease

Medical News, BMJ, 293, 1445, 1986

To illustrate the kind of misinformation which victim-oriented reporting can generate, have a look at the following headline in the USA: "411 DIE ON HIGHWAYS DURING LABOUR DAY WEEKEND".

First spontaneous reaction — How awful!!

An analytical look behind the headline:

50,000 traffic accidents occur in the U.S.A. every year, i.e., 137 per cent per day of 411 in 3 days. Since Labour Day weekend is 3 days, the 411 turns out to be the right average.

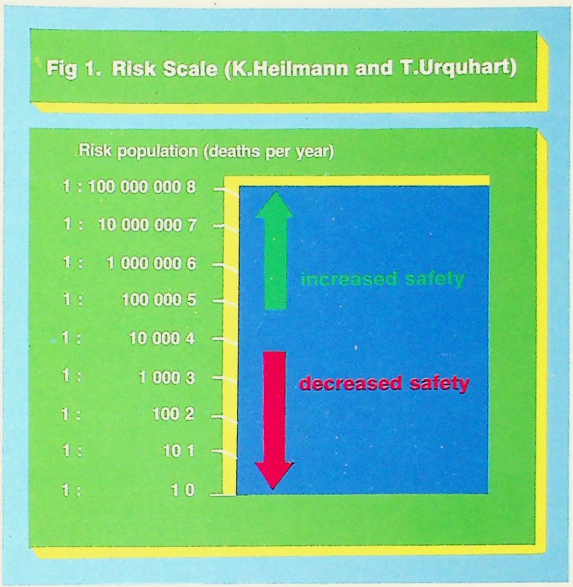
A closer analysis of that headline:

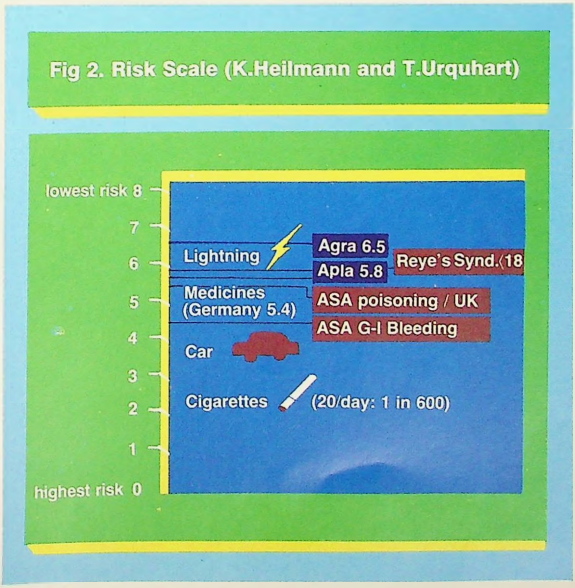
An average of 137 per day is misleading as there is a strong difference between weekday and weekend incidents. Monday through Thursday, the average number of traffic deaths is 75 per day. From Friday through Sunday the average number is 240 per day. In other words, a 3-day holiday weekend might be expected to produce $3 \times 240 = 720$ victims.

The alternate headline to the one above should have been "CAREFUL DRIVING ON LABOUR DAY WEEKEND — 309 LIVES SAVED." But human nature yearns for tragedy or bad news. Good news in our emotional makeup must take a second place.

Victim-oriented reporting is designed to leave us with anxiety and fear of such things in no particular order — the bomb, the next earthquake, a jet crash, a chemical plant fallout, passive smoking, AIDS. The list can continue endlessly, as long as it sells unpleasant events.

To give some order to these high risks, we must have a "Scale for risk" which integrates information so that rational people can make rational decisions about which hazards present high risks and which are accompanied by small risks.





The lack of acceptance of a uniform standard for expressing risk is one of the reasons that we haggle a great deal about certain risk-related issues.

Just as the Richter Scale in an earthquake report tells us about the severity of the quake, we need to have an analogous risk scale so that everybody can understand to what extent, for example, a newly discovered hazard affects our already known health risks.

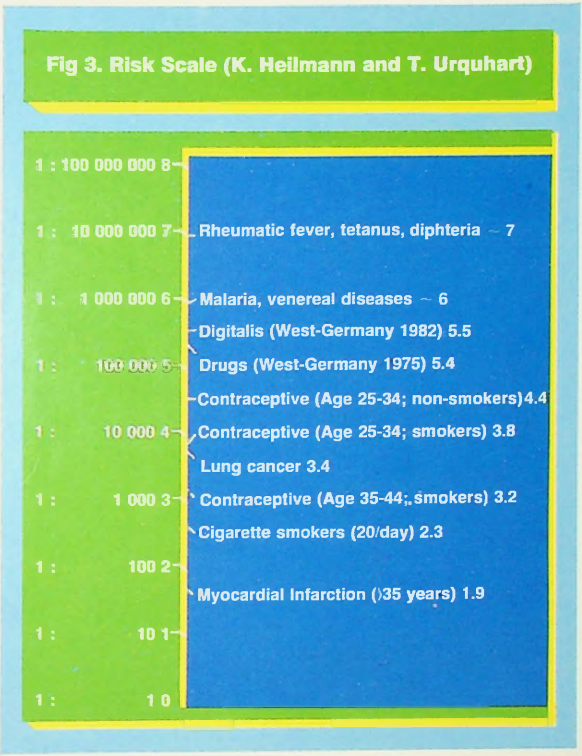
In making such a scale, it is important to keep it very simple. Instead of saying "the death rate from homicide in the USA is 10.4 per 100,000 per year", a simple way of representing this figure is by saying "the risk of one's dying due to homicide in a year's time in USA is 1 in 9615".

The number '1' means that the event in question happens to you or to someone else. The chances of '1' becoming a victim to a hazard is his or her risk.

The Risk Ratio is a ratio in which the numerator represents the individual who is actually harmed while the denominator represents the number of all persons who are exposed to the same activity but have emerged unhurt. For example, all airline passengers, all persons with high B.P., all cigarette smokers, etc. The risk ratio varies from 1 : 1 to 1 : 100 million representing a scale of 0 to 8 (Fig.1), where each number represents the number of zeros after 1. A 1 : 1 risk occurs when a person contracts a disease such as rabies which has the virtual certainty of death.

There is no theoretical upper boundary to the scale, but 8 represents this limit which has been set by the present methods of data collection. And so, now we see the basis for making easily understood statements such as "my risk of being killed as a passenger in an air crash is 1 in 800,000 per trip or, if using the above scale,the risk is between 5 and 6. Fig.2 compares the risk of various activities.

For greater accuracy any risk statement necessitates a time interval to be expressed. In general, either of two time intervals are used per year or per event, i.e., per trip or a surgical operation or giving birth or any such parameter.



Like all activities, drug treatment is also a calculated risk. HOW SAFE IS A DRUG? — this question is often asked. The safety of a drug is always assessed first by studies on animals and later in extensive clinical trials in human volunteers under regulated, approved ethically designed and closely monitored clinical trials.

The sample size required for detecting the occurrence of adverse drug reactions (ADR) varies and depends on the frequency of the reaction. If the frequency of the ADR is 1 : 10, then the number of patients needed to have noted this would be 39 - 40. Similarly,for a 1 : 100 ADR, 390 - 400 patients would have been required; for 1 : 1000, 3900 - 4000 patients and for a 1 : 100,000, a corresponding 390,000 - 400,000 patients. It is therefore almost impossible to detect rare ADR.

However, two kinds of studies to detect rare ADR have been epidemiologically identified:

a) The cohort type: Individuals likely to develop the disease are studied even before they suffer the pathology. They are followed up for prolonged time periods to determine when the exact occurrence takes place. This method obviously has tremendous constraints in terms of finance and time.

b) The case-controlled type: Every case identified is compared with a large number of controls who are necessarily matched for all identifiable variables with the suffering case. In so doing it allows the exploration of all possible causal factors related to the event, and also provides a numerically strong base against which incidence of the event can be compared. This kind of methodology is the basis of the International Study on Agranulocytosis and Aplastic Anaemia which has been presented in this issue.

One could use the Risk Scale to place some of the known side-effects of drugs in relation to other risks of life (Fig.3). As an example, the occurrence of agranulocytosis consequent to drugs occurs on this scale with a frequency so low that the chances of being struck by lightening or even encountering a car accident are very much higher.

Therefore the next time such a "sensational" news report appears,it would be very necessary to recall that the information is next to nothing if not presented along with the comparative data or the hidden facts.

Medicine and surgery are both naturally linked with risks. Contemporary medicine could never have brought solace to patients without the accompanying risks of therapy. Where would open-heart surgery, valve replacement and the like be today if the initial patients had not taken the risk of undergoing the surgeon's knife?

The risk of treating versus not treating is often the genesis to know how small risks can become the basis of big controversies.

The problem with drugs is not that their risks are greater than their benefits. It is simply that we cannot make up our minds about the risks — which risks are tolerable and which are not acceptable.

The tendency of people to worry about rare side-effects and forget about the benefit of the drug is due to our failure to calculate risks, to assess them and to compare them!

Prof. William Inman of the Drug Surveillance Unit of the University of Southampton has very aptly spelt out the benefits of a drug versus the risk of a drug-free existence, when he says "One way to consider drug risks is to ban all drugs. Ending all drug-induced harm would add 37 minutes to your life expectancy. Ending all drug-related benefits would subtract 15 years from your life expectancy, and also end the improvement in life quality drugs give".

Weighing Risks — A Case in Point

Many of us provoked to seek the aid of analgin for various aches and pains have often been perturbed by conflicting reports.

Analgin, which belongs to the family of pyrazolone analgesics, was discovered in 1918. Its discovery was an important breakthrough in the field of analgesics, since it offered doctors a safer alternative to the narcotic opiate analgesics like morphine and pethidine.

The worldwide response to the drug was astounding and it soon became the leading analgesic.

Somehow, through scattered, unchallenged reports, it began to be linked with 'agranulocytosis'. The essential mistake at the time was that these vaguely distributed reports were not investigated and proved then and there. These reports began to be repeatedly quoted as retrospective data and soon became the basis on which adverse effects of the drug were calculated and talked about. These few reporting incidents generated a snowball effect and analgin came under the strict control of the regulatory authorities in some countries. Incidence rates for agranulocytosis which were quoted as long back as 2 decades ago also became the basis to ban the sale of analgin in some countries.

Hoechst AG, at West Germany, being a manufacturer of the drug and concerned about the safety of its products immediately took steps to determine the true incidence of this disorder and assess the safety of analgin.

In 1979, a massive study was initiated in collaboration with the University School of Medicine at Boston, USA, to determine the true incidence rates associated with analgesics, not only for agranulocytosis, but also for the dreaded disease, aplastic anaemia, which has a fatality rate of about 50%. 300 hospitals from 6 countries (West Germany, Israel, Bulgaria, Hungary, Spain and Italy) covering a total population of 22 million people became the study base. A team of experts examined all laboratory material, i.e., slides of blood and bone marrow to reach a diagnosis independent of patient-history.

Besides Hoechst AG, this study, the first of its kind in the world and in medical epidemiology, saw participation very actively from the Governments of Sweden, Hungary and Bulgaria, the National Institute of Health, USA and the WHO.

Four long years elapsed before the data produced results. The International Study for Agranulocytosis & Aplastic Anaemia (ISAAA as it was called) would provide data on the drug-related causality of both these blood dyscrasias.

At the IIIrd World Conference of Pharmacology & Therapeutics, Stockholm, the ISAA study results were finally presented. The findings clearly revealed that the past doubts on analgin's safety had been needlessly raised and the previous incidence of agranulocytosis was grossly exaggerated. The originally quoted incidence for this disorder was the astounding figure of 0.8%. i.e., 8000 cases per million population!.

This error in previous calculations is totally mind-boggling — consider therefore with such an enormous figure, the incidence of analgin-related agranulocytosis in Bombay city alone should be of the order of 56,000 cases.

Dr. Samuel Shapiro, member of the ISAAA Study Group, accurately summed up this high-blown error when he stated at Stockholm last year that "the original estimates of agranulocytosis was an error of many orders of magnitude."

In fact, the study data presented showed that the risk of getting agranulocytosis following analgin was as low as zero to a maximum of one in one million users.

Along with analgin, the study also showed that a few other drugs like sulphas and commonly used analgesics have the potential to cause agranulocytosis, the commonest being indomethacin, which is surprising because this substance was never suspected to be a high-risk factor to get agranulocytosis. Moreover, indomethacin also was associated with aplastic anaemia. This disorder is unrelated to the use of analgin.

At this conference, it also became evident that other major pain-killers, like aspirin bear the risk of rare but severe adverse drug reactions. The risk of gastrointestinal bleeding is substantially increased often to a fatal end. Aspirin was also associated to an appreciable extent with aplastic anaemia. With paracetamol, the other common pain-killer, no association with either disease could be found, but the experts stated, there were not enough cases of individuals exposed to the drug.

Analgin is almost 65 years old. Yet it continues to successfully vie with its younger competitors for the pride of place among not only pain-relieving drugs, but also among fever-reducing agents because it has the twin combination of proven safety and efficacy.

According to Dr. T. Floeter, Doctor of Anaesthesiology who runs a Pain Clinic in Frankfurt, "Analgin is irreplaceable among peripheral analgesics. Its therapeutic uses are so broad and yet no case of poisoning has been observed".

Current research indicates that the drug is superior to aspirin and paracetamol for the relief of pain and fever.

All analgesics, like any drug, have some element of risk involved with their use because they, like any other drug again, can cause a hypersensitivity reaction in an isolated patient, but this is an extremely rare phenomenon and the side-effects which are usually talked about so loudly are so extremely rare that most doctors have an occasion to learn about them only from textbooks.

Any drug at any time is always a risk to the user, and drug-related risk is always a concern. A risk-free drug has yet to be found and therefore every drug needs to be evaluated not on the isolated case of adverse effects, but on the vast population who will benefit from its use. Therein lies the answer to what is colloquially known as the risk-benefit ratio!

Acute Myocardial Infarction (AMI)

Approximately 40-50% of persons who suffer an acute myocardial infarction die within 20 days of the onset. If one takes into consideration that half these deaths occur within the first and second hour after the onset of the symptoms, the urgency to provide prompt treatment is further stressed by the fact that the majority of these deaths are due to potentially correctable ventricular fibrillation.

The most common presenting feature in more than 80% of patients is severe pain in the retrosternal area of the chest or epigastric pain. Precipitating factors such as a heavy meal, emotion and exercise may have triggered off the attack but, in many cases, AMI occurs at rest. The patient often describes the pain as having the same qualities as those during an anginal attack,but being of a more severe and persistent nature which does not respond to nitrates. Radiation to the neck, jaws, arms and fingers is commonly encountered.

Persons having no prior history of cerebrovascular disease may ascribe the pain to indigestion, as belching and nausea frequently accompany an attack. Sweating, weakness, giddiness, anxiety and restlessness can also be present. The intensity and quality of the pain varies with different individuals and, in 10-20 per cent, pain may not occur at all. This has been noted with greater frequency in diabetics.

The patient is usually in obvious distress, anxious, fearful and pale. Physical examination may reveal only a weak thready pulse and the B.P. low — though a transient rise due to anxiety and fear can occasionally be found.

On auscultation, a fourth or atrial sound is present and may be palpated as a presystolic expansion over the anterior aspect of the left ventricle. With extensive myocardial damage, a third heart sound is present often accompanied by a systolic thrust palpable over the 3rd and 4th intercostals.

Differential Diagnosis

The clinical history of AMI is straightforward; with a careful examination and history, the following should be ruled out:

1. Aortic dissection
2. Pulmonary embolus
3. Pericarditis
4. Spontaneous pneumothorax
5. Acute pancreatitis
6. Spontaneous rupture of oesophagus
7. Peptic ulcer
8. Cholecystitis

Management

1. Immediate slow intravenous injection of morphine 10-15 mg results in rapid pain reduction and reduces anxiety. Pentazocine is not recommended as it may induce hallucinosis and cause a rise in pulmonary artery pressure. Morphine has an advantage in that it causes peripheral vasodilation; postural hypotension and bradycardia may result due to this, but is rare and requires only postural readjustment. Other alternate analgesics are diamorphine, pethidine and methadone.

   If potent analgesics are not available, a 50% nitrous oxide/oxygen mixture can reduce pain and distress; this can also be used during transport to a hospital.

2. Examine cardiovascular system, especially pulse, B.P. and heart sounds. If possible take an ECG:
   a) If pulse is less than 45/minute, atropine 0.6 to 1.2 mg intravenously or intramuscularly may be given, especially if hypotension is also present.
   b) If pulse is irregular an intravenous bolus of 50-100 mg xylocaine or lignocaine can reduce the occurrence of potentially fatal arrhythmias.
3. If cardiac failure is present, 80 mg frusemide should be given.
4. If patient deteriorates and goes into ventricular fibrillation, defibrillate at once. Perform external cardiac massage and mouth-to-mouth resuscitation.
5. Admit immediately.

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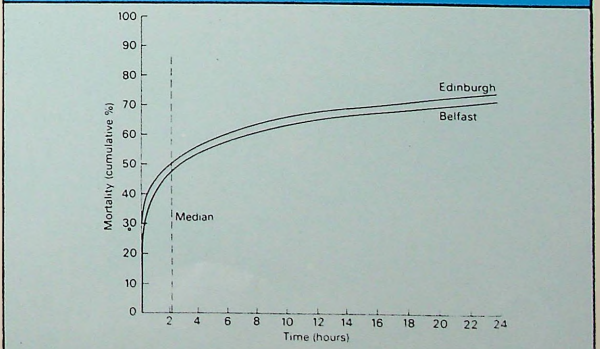
Cumulative percentage mortality in the first 24 hours after the onset of symptoms of myocardial infarction.



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Convulsions in Children

To be called to a child having a convulsion is a disconcerting experience. Often by the time you reach him the fit is over. If it is not, all you need do is to prevent him hurting himself. When the jaws are already in spasm you may cause damage by forcing them open but a gag may be used if the airway is obstructed. The parents will be alarmed and it is important to behave in a reassuring way. Let them see that you know what you are about. Prevent them from doing silly things. It is comforting to them to see a cold compress being prepared and even to help you or Sister to put it on the head. In the rare case where fits continue without a return of consciousness (status epilepticus) they must be stopped, for prolonged convulsions are incriminated as a cause of temporal lobe epilepsy. Give diazepam 5 to 10 mg by slow i.v. injection or rectally. An alternative is paraldehyde 0.1 mg/kg i.m. which can be repeated after an hour, or, phenobarb 6 mg/kg i.m. Remember that a plastic syringe cannot be used for paraldehyde. After the fit is over try to find the cause. This varies with the age of the child. In the newborn birth injury is likely. Hypoglycaemia should be looked for because it is easily missed and otherwise disastrous. In the toddler febrile convulsions are common and in the older child epilepsy, intracranial disease (meningitis) and nephritis should be thought of. About 1 child in 15 has a convulsion and at least one-third of these are simple febrile convulsions. So be reassuring to the parents. The outlook is good if the child is mentally and structurally normal and if the fits are brief, albeit recurrent, complications of a febrile illness ('benign febrile convulsions') as distinct from true epilepsy precipitated by fever.

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The House Physician's Handbook C. Allan Birch, S.J. Surtees, Richard Wray, Fifth Edition, 1980, Churchill Livingstone, p. 247.

In a Lighter Vein

THE PAIN SYNDROME

A pain sensation pulls a person immediately into an isolated orbit in which he remains alone with a personalized experience, since pain is a very private sensation. An individual may try to express pain verbally or through behavioural changes which may not however convey the actual sensation or intensity of pain. This makes pain an essentially abstract concept, though it is a very tangible hurt — a hurt that can be only insufficiently communicated. Besides, pain *per se* is seldom uniform in its effect on people, because of the structural differences among them, the differences in their levels of tolerance as also in their attitudes which condition their total perception of pain.

The Role of Pain Expressions in Medical Diagnosis

Expressions of pain are of immense value in medical diagnosis. The physician is heavily dependent on the patient's report of pain, its nature, location, intensity, duration and so on. By the virtue of the power of articulation and expression, human beings are better subjects than animals for the study of pain.

The study of pain is difficult as not all aspects of pain are available for scientific enquiry. However, externalised 'behaviour' due to pain is observable and therefore can be described in visible terms which makes it less of an abstract concept. Signs of writhing, gritting of teeth or withdrawing from pain, for instance, may find supportive verbal expressions to describe the agony one feels. Pain can be described in neurological or in psycological terms. By recording the verbal signals of pain, medical science is greatly assisted in discriminating varieties of pain, both in their nature (muscular ache, scalding, burning, stabbing, smarting, throbbing) and degree (severe, mild, bearable, etc). Although these may be clothed in culturally defined styles,one can nevertheless zero in on certain features to deduce the nature/source of the pain.

Pain as a Defence System

Pain promptly set up an alarm to the brain, putting it on the alert about harmful, external influence on the body. This new perception of pain as a warning and a protective reflex alters its role from a negative concept to one of extreme importance, since it attempts to protect the body. This can even be seen in the effective way in which a reflex withdrawal prompted by a burn or an electric shock, minimises injury.

Pain Receptors

Pain signals are picked up by nerve endings which are called pain receptors. They mediate a response signalling pain impulses to the brain and setting off the first alarm that something is wrong with some part of the body. The central nervous system helps locate the source of the pain. Pain receptors are of various types, each of which responds to a different sort of tissue damage, such as from a cut or that caused by heat or chemicals. It is important to remember the same kind of pain may evoke varied intensities of responses from different individuals, depending upon the individual degree of pain tolerance and the pain threshold.

Kinds of Pain

Pain sensations are of various types. For instance, a sprain in the leg feels different from the sharp pain due to an abrasion; a pervasive toothache feels different from a burnt finger or a headache. Pain varies in duration too. It can be intermittent, prolonged or even chronic; in some cases, it may persist for months or years, disrupting the lives of the suffering individuals. There is also the "referred pain", a situation in which an area of the body may indeed hurt, but the real origin of the pain may reside elsewhere, in a region far removed from the area. This

"referred pain" can lead to an error in localization.

Kinds of Pain Responses

There are as many kinds of pain responses as there are kinds of pain. To cite some, neurological, physiological, verbal, behavioural and "affective" responses to pain exist. From the medical point of view, physiological responses are more reliable than verbal expressions; changes in blood pressure, heart rate, dramatic changes in muscle tension or sweating, help in arriving upon objective data. And yet, medical diagnosis does not underestimate the "affective" descriptions of pain as they come closest to the essentially personal experience of pain and its uniqueness. All the classifications talked about earlier — physiological, neurological, behavioural, "affective" — are confusedly abritrary, whereas in reality they are mutually inter-related and integrated by the individual who experiences pain. Classifications that go against this holistic view of pain are only resorted to as clearing-aids for medical diagnosis and treatment.

A Puzzling Phenomenon

When pain enters a less tangible plane, it becomes more challenging for the medical profession to alleviate suffering. There are three puzzling phenomena of pain which are identified — insensitivity to pain, phantom pain and the hypnotic relief of pain. The first is by no means a blissful condition,for often persons who fall in this category have other associated neurological defects. The second, 'phantom pain', may occur in a non-existent location as in the imaginary pain in a leg which has been amputated long ago. Hypnotic analgesia is another area which causes a patient to accept even the worst, whatever illogic it involves.

Conditioning

The familial, social and cultural environment along with temperament and personality 'condition' a person. A neurologist, physiologist or psychologist is each dependent for his data on the patient's cultural conditioning, upbringing, and discipline. For example, the Irish are supposed to be inhibited in their expressions of pain,while the Americans tend to "take pain in their stride" (which is believed to result in less anxiety and higher tolerance). Certain ethnic groups like the Jews and Italians implicity encourage complaints of pain, while others discourage it.

Apart from cultural conditioning, personality traits, such as an extraverted nature, results in relatively low anxiety states, whereas a neurotic temperament produces greater anxiety. Pain tolerance also varies with the presence or absence of sympathy from the family or attendants.

Pain Threshold

Pain threshold (which is not quite the same thing as pain tolerance) is roughly the same in all people even from diverse ethnic groups. In patients with "low painful threshold," pain occurs with negligibly painful stimuli, while those with "high painful threshold" may bear severely painful stimuli uncomplainingly. Extreme stress and shock are also known to numb pain, for the brain manufactures its own opiates, resulting in what is medically termed as "stress–induced analgesia."

Coping with Pain

Coping with pain involves a thorough understanding of the pain situation which, in turn, requires education not only in the endurance of pain, but in understanding the limitations of preferred relief as well. Two old methods for minimising pain are application of heat or cold compress to give a temporary respite from pain. Massages and exercises have also been tried. In electrical therapy, electrical impulses of adjustable intensity and frequency are applied through small skin electrodes to stimulate (cutaneous) nerve endings and muscle fibres. This treatment, however, is known to give relief only as long as the stimulation is continued. Surgical measures of pain relief are undertaken in extreme cases. Acupuncture is an ancient treatment where needles inserted into 'acupuncture points' relieve pain. Psychotherapy sets about to change thoughts and ideas of the patient simultaneously, and obliquely appealing to the patient's will in coping with pain.

Pain Relief

Treatment in medicine has one major aim — to relieve suffering. Anaesthetics make surgery possible without pain by preventing pain signals from reaching the brain.

Local anaesthetics block the sensory nerves which conduct pain. In addition to anaesthesia are a variety of substances that help in the safe elimination of pain. Analgesics like asprin, analgin and paracetamol are given in effective doses and are sometimes also given in anticipation of pain. It is when it comes to chronic diseases that the benefit-risk ratio of drugs must be carefully weighed.

Modern therapy has now stretched to para-medical areas. Ordinary, everyday work is in fact looked upon as an occupational therapy. Modern medicine, therefore, drastically curtails the duration of convalescence. It encourages the patient to get on to his feet as fast as he can and on to his work environment for that will surely help in dispelling his pain symptoms.

Doctor-Patient Relationship

This relationship is so important that it could be the cornerstone of therapy. The doctor should acknowledge the reality of the patient's experience, encourage the patient to express himself and show a willingness to understand what he says. Medical ethics has developed enough to understand the obligatory need to give a patient all the information he needs regarding his condition.

Knowledge of his condition may help the patient regain his confidence and reduce his anxiety. For a good doctor-patient relationship, it is equally important for the patient not to be passive but responsive and co-operative with the doctor who is, after all, trying hard to contend with the pain as much as the patient does.

Pain is a reality. There is now a more comprehensive, holistic view of pain than before, which takes into account the patient's mental agony together with his physical suffering.

Medicine no longer dismisses intractable pain as "psychological" nor does it like the idea of making a patient toss between "psycho" and "somatic" evaluation. It realises that it is our thinking here which is dichotomised and not the pain sensation in itself, which is inherently physical, mental, psychic and somatic, all in one.

Glimpses from Literature

Analgesics in the Management of Pain

The management of pain, especially chronic pain, presents a complicated problem as it becomes an illness in itself. This is amply bourne out by the average number of years — over 10 — and by the number of doctors seen — 8 — by the patients who come to the Pain Clinic run by Dr Floeter in Frankfurt.

Important in management is the analysis of pain, namely, its origin, i.e., whether central or peripheral, the intensity of the pain, its exact location and the pattern of the pain. Depending on this, the choice of an analgesic of central or peripheral action, potent or mild, and the need for additional local treatment is determined.

Of the non-narcotic analgesics, dipyrone or metamizole or analgin is the single most important drug due to its very wide therapeutic index or safety margin, its effectiveness and the combination of analgesic, antipyretic, anti-inflammatory and antispasmodic properties. All these complement each other in pain management, for example, the relief of pain in biliary or renal colic is assisted by its antispasmodic action.

It is, however, not only the total number of properties alone that is decisive, but also the consideration of side – effects and potential for abuse. Aspirin, which is important in pain management and useful for its antithrombotic effect with low doses loses its usefulness at high doses because of its serious G.I. effects. Similarly with paracetamol, high doses and long-term use are frequently associated with liver damage.

Dr T Floeter, The Indian Practitioner, 1987, XL, 1

Red Blood Cell Defect Linked to Deafness

Plasma viscosity, in a study of 140 people from a hearing clinic and the general population, was found to correlate with hearing loss; lower plasma viscosity correlated with higher degrees of hearing loss. This finding was a surprise to the researchers, Dr. George Browning and colleagues at the Medical Research Council's hearing research unit in Glasgow; they had thought that if blood was more viscous, supply to the tiny vessels supplying the hair cells (stria vascularis) may be impaired, leading to ischaemia and death of hair cells.

The unexpected finding led to the discovery that the variable most closely linked to the degree of deafness was red cell stiffness; stiff red cells get stuck in the tiny vessels in the inner ear, leading to ischaemia, death of hair cells and possibly even atrophy of the blood vessels themselves. The lower viscosity of plasma in people with stiffer red cells is probably due to a homeostatic mechanism to keep the overall viscosity of the blood near normal values.

The cause of the red cell stiffness, whether primary or secondary, is not known. However, the finding makes a strong possibility for treating and preventing sensineural deafness in the future.

General Practitioner, 24 January 1986, 2

Major Upper Gastro-Intestinal Bleeding in Relation to Aspirin and Acetaminophen Use

Upper gastrointestinal bleeding (GIB) is a relatively common illness. Three countries — the USA, Canada and Israel conducted a hospital-based case-control study to examine the relationship between aspirin or acetaminophen use and GIB.

57 persons were admitted with major GIB. None of them had any earlier known predisposing factors for GIB. They were matched with 2417 patients admitted at the same time for conditions judged to be independent of prior analgesic use. The latter served as controls. Drug use was specifically investigated for the week prior to the day on which symptoms of the disease first occurred.

The results show that regular use of aspirin — for at least 4 days — entails hospitalization for major GIB in at least 82 patients per million users. Occasional use of aspirin caused major GIB in 25 persons per million users.

Even the common non-steroidal anti-inflammatory drugs had an elevated risk of upper GIB, but evaluation of individual drugs was not possible because of insufficient data.

III World Conference on Clinical Pharmacology and Therapeutics, Stockholm, Abstracts II, 1986, 326

Clinical Evaluation of Drugs Used in Fever

Fever, especially when high, has many metabolic and haemodynamic effects; for example, the metabolic rate rises by 15 per cent for each degree Celsius rise in temperature. At the same time, the food intake reduces. This results in the catabolic processes becoming predominant and thus an essential need for antipyresis.

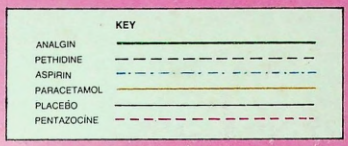
As aspirin has limited use in a febrile anorexic patient due to its gastrointestinal side-effects, paracetamol and analgin were compared for antipyretic efficacy at the Kasturba Infectious Diseases Hospital, as they both have clinically insignificant gastrointestinal side-effects.

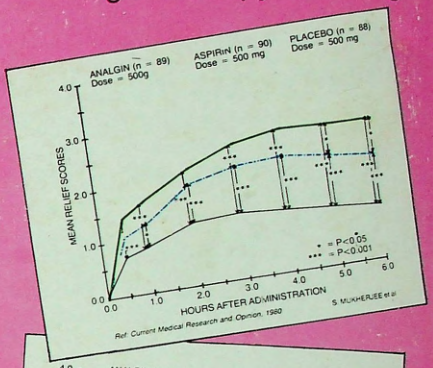
Adult males, clinically considered to have enteric fever, with a rectal temperature of over 38.2°C were studied in a random, double-blind fashion. Fever and pulse rate were continuously monitored by a computerized machine for 8 hours and thereafter manually for 4 hours. Hepatic and renal function were evaluated prior to the study and after it.

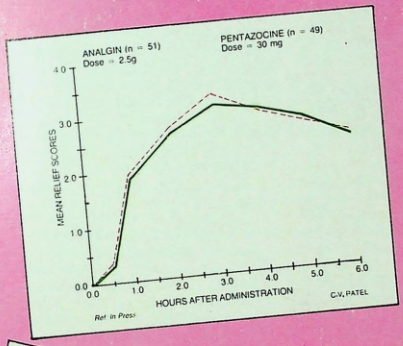
In a preliminary double-blind, placebo-controlled study, the effectiveness of 1 gm analgin as an antipyretic was established, but the occasional diaphoresis seen in some patients suggested the dose may be too high in Indian subjects. Therefore, in a subsequent study, 500 mg analgin was compared with an equivalent dose of paracetamol. The onset, degree of antipyresis and total duration of action were significant in favour of analgin.

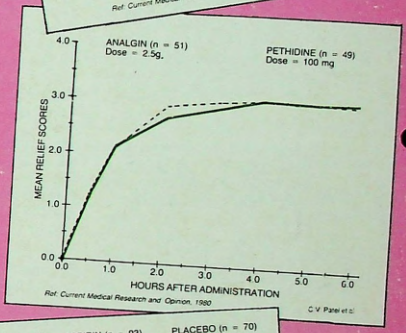
V.S. Ajgaonkar, The Indian Practitioner, 1987, XL, 29

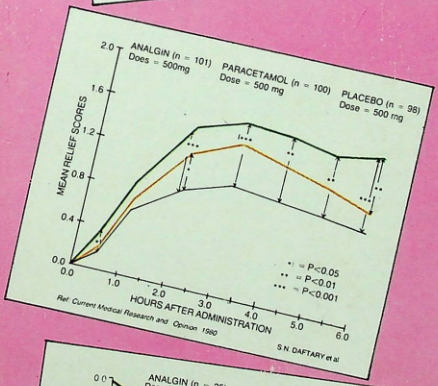
Recent Indian Research on Non-Narcotic Analgesic Antipyretic Drugs

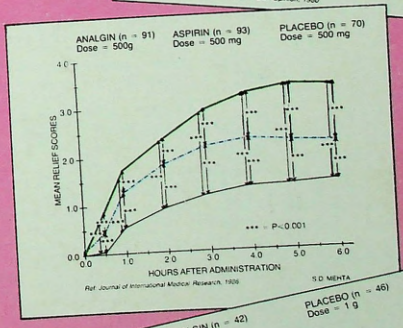


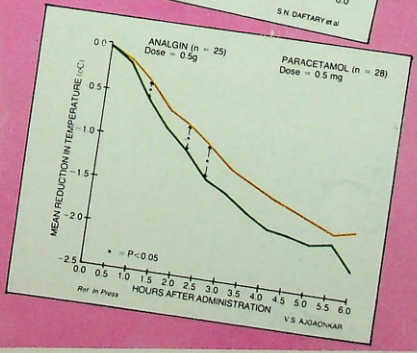


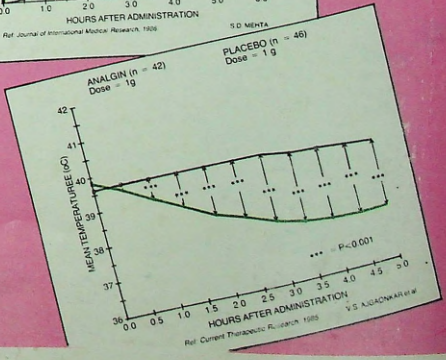












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ANALGIN - A STUDY FOR DRUG ACTION FORUM-KARNATAKA

1. The Drug

A class of chemicals called PYRAZOLONES have been used as medicines for over ninety years. Pyrazolones include drugs like **Anti Pyrine, Aminopyrine, Phenyl Butazone, Oxyphenbutazone, Sulfinpyrazone** and a derivative of **Amine-pyrine** called **Dipyrone** or **Analgin.** The pyrazolones share similar pain-killing, fever-reducing, inflammation reducing and also toxic properties. Analgin being more water soluble is amenable to use in injections and liquid oral preparations (for children). They are rapidly absorbed in the stomach and intestine and spread in various tissues of the body in proportion to their water content. While 30 to 40% of the drug is altered in the liver and eliminated in the urine, 5% is eliminated unaltered. The fate of a significant fraction is not known.

The range of actions of Pyrazolones is similar to that of Salicylates (Aspirin) except in reducing fever in diseases like Hodgkins disease and Periarteritis nodosa, where aspirins are not completely effective.

The most important and potentially fatal adverse effect of Pyrazolones (Analgin) is **Agranulocytosis.** This is a condition where the Granulocytes which form the major part of the White Blood Cell population and are the first line of the body's defence against infection are destroyed. It is an allergic reaction and can occur suddenly even after a fraction of a dose in any person who has been previously taking Analgin with no bad effects. Within 6 to 24 hours, the while blood cell count fall and granulocytes disappear from the blodd. They start re-appearing 5 to 10 days after the drug is discontinued and rapid recovery occurs. The incidence of agranulocytosis has been variously estimated from 0.01% to 0.86%. If infection occurs now, it starts as a sore throat of sudden

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8. Dipyrone, Hoechst and the Boston Study, MFC Bulletin Dec 86
- Wilbert Bannenberg

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- Trisha Greemhalgh

10. Dangereus and Inappropriate drugs
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onset, high fever and prostration, which even on proper treatment carries a mortality of 20 to 50%.

The other adverse effects of Analgin documented in a study are, skin rashes, Dyspepsia, Fever, Anaphylactic shock and Bronchospasm. Analgin can aggravate a bleeding tendency and produces a serious fall in body temperature when given along with Chlorpromazine. Liver cancer in mice has also been reported by Japanese.

Even now

a. the mode of action is not known;
b. which are the metabolites which cause agranulocytosis and how is now known;
c. Basic pharmacological data, like potential for causing Cancer, congenital malformations, kidney and Liver damage and damage in elderly patients are not known;
d. Interactions with other drugs for diabetes, hypertension etc., have not been investigated – because Pyrazolones were introduced in the pre-Thalidomide era when registration was easy.

2. History and Present Status

1897 - Aminopyrine was first introduced and became very popular in 1920s for painkilling and fever. By 1930s it's use was world wide
1922 - Agranulocytosis was first described by W. Schulz.
1922 - Dipyrone or Analgin was introduced by Hoechst, Not being recognised as a derivative of Aminopyrine, it gained popular use.
1933 - Madison and Squier established a causal relation between Amidopyrine and agranulocytosis
1935 - Kracke and Parker established its relationship to agranulocytosis beyond doubt
1938 - O.T.C. sale in U.S.A was prohibited

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Between 1955-59 - The American Medical Association Registry on Adverse Reactions recorded only 10 reports of leucopenia (fall in W.B.C count) and none in children

1960-64 - 18 cases reported (7 in children)
An increase in the import into U.S.A of dipyrone from Nil in 1958 to 18,879 lbs in 1962 was noticed.

1964 - Americal council of drugs - section one adverse reactions studied the case of Dipyrone (Analgin) and questioned the justification of continued use of this drug.

1960 - Great Britian and Canada revoked the licence of Dipyrone

1965 - Australia and New Zealand issued an import ban on dipyrone

1974 - Sweden revoked Dipyrone licence

1976 - Norway revoked Dipyrone licence

1977 - U.S.A revoked Dipyrone licence

1977 - Japan banned free O.T.C sale

1978 - Ireland and Singapore revoked licence of Dipyrone

1979 - Denmark revoked licence of Dipyrone

1986 - Malaysia banned dipyrone

1980-84 - An international study for Agranulocytosis and Aplastic Anaemia was done in Europe - called the Boston Study, since coordination and data analysis was done at the Drug epidemiology unit at Boston, This was primarily financed by Hoechst, and the results published in the JAMA of Oct 1986.

1983 - The G.D.I banned the manufacture and sale of Amidopyrine.

1986 - Malaysia banned dipyrone

1986 - F.R.G banned O.T.C sale

In Netherlands, Dipyrone use is only allowed for uncontrollable fever.

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following reports of anaphylactic shock, Italy, Egypt and Saudi Arabia have prohibited manufacture of injectible preparations

The F.D.A of U.S.A regards that "true risk associated with this drug far outweigh any benefit derived from its use, including use in Hodgkins and similar malignant diseases".

3. The Issues

i. According to Hoechst, approximately 25 tonnes or 18.5 million doses of Novalgin are used world wide everyday. With most of the developed nations banning or restricting its use, it is obvious that it is sold mainly in third world countries.
The countries which have banned Dipyrone have been managing pain without Dipyrone by using equally effective and sage analgesics.

ii. The 'Boston Study' generated a lot of controversy, since Hoechst used the results even before publication for a misleading advertisment campaign showing the occurence to be 1 per million. The Hearing of the German Federal Health Office finally confirmed the assumption of 1 per 30,000 to 60,000 to be nearer the mark, or one tablet per 70,000 consumed could cause agranulocytosis based on this same study.
The limitations of this study are, that

a. it excludes all patients
   i. who die of agranulocytosis without receiving medical aid;
   ii. who die without having a white cell count, and
   iii who have undiagnosed agranulocytosis and recover from it.
b. The study does not look into other side effects of Dipyrone, like shock, fall in B.P., Urticaria etc.

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c. The data presented in the intermediate and final reports are inconsistent.

d. Whereas 400 cases of agranulocytosis were registered to assess risk properly, only 221 cases were analysed in the final report, and

e. There is extreme variability in data between different countries and even within the same country.

f. Some data were seen to be clearly unreliable.

iii. The findings of the controversial 'Boston Study' is being utilised by Hoechst the largest manufacturer of Analgin for sales promotion in Germany, Eastern Bloc Countries and the Third World. Unethical propoganda practices with different types of promotional literature in different countries is being practiced.Even claims of anti-spasmodic action which is not scientifically substantiated is being made. Any source of detailed scientific literature is virtually non-existant beyond the literature supplied by the drug companies.

iv. Since 1985, Dipyrone (Analgin) has not found mention in any standard medical text books, except for naming it as a drug which can cause agranulocytosis.

v. Even in our country, Medical students do not learn about Analgin while doing their Pharmacology.

4. In India

1. In 1983, the G.O.I banned the manufacture and sale of Amidopyrine but not dipyrone. The Drugs Consultative Committee had recommended ban on FDCs of dipyrone also, but this seems to have slipped from the banned list.
2. The Government is the largest manufacturer of Dipyrone in this country.

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3. Analgin is among the largest selling analgesics in the country with sales figures accounting for Rs. 70 million. There are approximately 200 formulations containing Analgin, including injectables, and drops for newborns and infants for colic.

4. Analgin is available as O.T.C inspite of its being a Schedule H drug in our country and the attitude of the prescribing doctors as per a study (Lancet 86) was "if I prescribe it 30 times a day and it is available over the counter it must be safe". In a field study (Lancet 86) it was seen that the pyrazolones made up the majority of both G.P prescriptions and O.T.C sales of Analgesics. One more of these drugs were given to over 50% of patients requesting an analgesic.

5. Drug action groups have initiated a campaign on Analgin especially at ACASH, Bombay, DAF West Bengal and AIDAN, New Delhi.

6. Analgin induced agranulocytosis does occur in India, especially if one looks for it systematically as a Bombay haematologist B.C.Mehta has done. He reports 12-15 cases of agranulocytosis a year, of which 10-12 are caused by Dipyrone or Dipyrone containing drugs. Even by the risk estimation of the Boston Study, in India, one person develops Analgin induced agranulocytosis per day by other reasonable estimates, it could be 15 times this figure.

5. Wider issues

Developing countries like ours are ill placed to afford expensive and useless health care products and definitely not the frankly dangerous ones.

We have unsophisticated consumers and poorly developed regulatory and advisory systems - this is fertile ground

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for pharmaceutical companies to indulge in unacceptable practices.

The vast majority of rural doctors working in professional isolation have no access to independent information on drugs they prescribe. Here, the representative of the pharmaceutical company who is ill-informed himself and paid by commission on drug sales becomes an ideal tool to promote the interests of the Pharmaceutical company.

Thus, it appears that the consumer is at the mercy of drug manufacturers. Other than an appeal to the Food and Drugs Administration, the Central government and the MRTP Commission the consumer is virtually without recourse to any independent body such as the judiciary. The J.J Hospital Commission (Lentin Commission) enquiry reveals the ineffectiveness of these agencies. The consumer protection Act of 1986 is expected to offer some hope.

In effect, only a public outcry by the consumer can force Voluntary withdrawal by or reform by drug companies.

— SP Tekur

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   Drug Disease Doctor Vol 3, No 4 1988
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product—sphingolipidoses (eg, Tay-Sachs disease), mucopolysaccharidosis (eg, Hurler disease), glycoproteinoses (eg, fucosidosis), mucolipidoses (eg, I-cell disease), and type II glycogenosis (Pompe disease). Acid hydrolase deficiencies are due to a series of single-gene mutations with the following results: failure to produce immunologically detectable enzyme glycoprotein (CRM^+); production of catalytically inactive or inefficient protein (CRM^+); reduced or absent post-translation processing of the enzyme protein; excessive post-translation processing; failure to glycosylate the enzyme protein; failure to generate the mannose-6-phosphate recognition marker which enables the enzyme molecule to follow its correct path to the lysosome after it has been glycosylated in the Golgi apparatus; lack of an enzyme activator or protector protein; lack of a substrate activator protein.

Each of the main types of gene-product abnormality can be due to several different abnormalities at the genomic level. Thus CRM negativity may be due to a lesion of the gene directing the synthesis of the enzyme protein (and this can itself be due to premature insertion of a termination codon, deletion of a major portion of the gene including the coding region for the immunogenic site, mutation or deletion of a start codon, or a splice-mutation); transcription failure; translation failure. The CRM^+ variants of these diseases show a similar range of genomic lesions which modify the activity of the catalytic site on the enzyme molecule without altering the immunogenic site. In addition to, or instead of, modifying or abolishing the catalytic site, the genomic lesion may lead to an abnormal gene product (the enzyme) with reduced affinity between subunits, reduced stability, increased susceptibility to proteolysis, or reduced solubility with impaired mobility in the reticular system and Golgi apparatus. Lack of an enzyme activator or protector protein, or of a substrate activator protein, can be the result of a similar range of genomic lesions. Lysosomal storage diseases that are due to lysosomal acid hydrolase deficiencies have now been reviewed in a monograph[13] and the biosynthesis and intracellular migration ("trafficking") of these enzymes have been intensively studied by several groups of workers.[14,15]

In Salla disease[16] there is abnormal lysosomal storage and urinary excretion of N-acetylneuraminic (sialic) acid,[17] and the disorder was provisionally grouped with the glycoproteinoses.[18] It is now clear that the disease is attributable to a transport defect whereby sialic acid cannot be transported out of the lysosome.[19,20] Salla disease is an autosomal recessive disorder which appears to be confined to individuals of Finnish descent, and which derives its name from the region of Finland whence most of the patients have originated. Patients show muscle hypotonia and psychomotor delay by 4–12 months of age; motor incoordination, dysarthria, dyspraxia, and mental handicap then become apparent. Some patients have epileptic fits and muscle rigidity, torsion dystonia, and signs of an upper motor neuron lesion may be apparent later. Salla disease is the first disorder shown to be due to defective transport of a monosaccharide across the lysosomal membrane. The findings are consistent with sialic acid egress from the lysosome being mediated by either a diffusional or facilitated transport system, but it has not yet been possible to demonstate the saturability of the system which is required to establish the existence of a specific carrier mechanism or carrier protein. Nevertheless, there is some circumstantial evidence for the view expressed by Renlund et al that "a single gene product, a specific carrier, mediates the transfer of NANA (sialic acid) across the lysosomal membrane".[20]

Cystinosis is no longer the exception among the lysosomal storage diseases but the archetype of a new subset of these disorders, and a disease due to defective transport of vitamin B_{12} across the lysosomal membrane is already known.[21] One family has been identified in which a lysosomal hydrolase deficiency (Fabry disease) and a lysosomal transport defect (cystinosis) occurred in different members of the same sibship.[22] The lysosomal transport defects may well prove to be as important and varied as the diseases caused by deficiencies of lysosomal hydrolases.

ANALGESICS, AGRANULOCYTOSIS, AND APLASTIC ANAEMIA: A MAJOR CASE-CONTROL STUDY

AGRANULOCYTOSIS and aplastic anaemia are rare but commonly fatal complications of drug treatment. Their rarity has made it difficult to assess the risk associated with individual drugs; estimates have often been alarmingly high or complacently low. Now the first findings from a large case-control study offer some answers about analgesics.[1] The impetus for the work was a stark difference of opinion about the safety of the pyrazolone analgesic dipyrone. As we noted last month,[2] Hoechst, the major manufacturer of the drug, needed clear evidence that it was acceptably safe, and so sponsored the independent International Agranulocytosis and Aplastic Anaemia Study. Funds were also contributed from Hungary, Bulgaria, and Sweden. The

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study was coordinated and the data analysed by the Drug Epidemiology Unit in Boston and supervised by a distinguished honorary advisory board.

The study aimed to collect all cases of agranulocytosis and aplastic anaemia that were admitted to hospital (community cases) or that occurred during a stay in hospital (hospital cases) in each of seven regions—Israel, Barcelona, Ulm, West Berlin, Milan, Budapest, Sofia, and Stockholm/Uppsala—with a total population of 22·3 million people. The attempt to include the region of Sao Paulo failed. Great care was taken to prove the diagnosis. Detailed drug histories were obtained from the patients, focusing especially on the seven days before admission (agranulocytosis) or on the preceding six months (aplastic anaemia). The interview included presentation of a long list of generic and brand names. Controls for the community cases were selected from patients admitted to the same hospitals, but the prospective controls for the hospital cases were too ill to be interviewed. Conclusions about individual drugs had to be based on the community cases alone.

The annual incidence of verified cases of agranulocytosis ranged from 1·7 to 9·0 per million in the different regions. This of course excludes mild cases that were not recognised and those that died before the diagnosis could be made. Some cases might also have attended hospitals outside the catchment area. The fatality rate was 10% among community cases and 6% among hospital cases. Regional fatality rates are not reported, perhaps because they might be taken to reflect differences in the effectiveness of medical care. The real meat of the report lies in the estimates of risk associated with different drugs. A rate ratio (rr) for each drug was obtained from the number of community cases and of controls who had taken it in the seven days before admission to hospital. One-third of the 300 community cases were excluded because they were not interviewed (21 had died), or because the day of onset could not be determined. For dipyrone, but not for any other drug or group of drugs, the rr varied greatly between regions, ranging from 1 and 2 (Budapest, Israel) to 21 and 31 (Berlin, Barcelona). These huge disparities raise some doubts about the results, for they were not due to differing incidences of agranulocytosis, but to very high and perhaps untrustworthy figures for dipyrone use by the controls in Israel and Budapest. Despite the low rrs for these two regions, 18% of their cases were apparently due to dipyrone, hardly less than the 23% in the study as a whole. Some of the doubts might have been resolved by examining sales data, but none were used—although Laporte, one of the investigators in the study, has presented such figures.[3] The estimate of the excess risk from dipyrone is expressed rather oddly, as 1·1 per million takers during a seven-day interval. The calculation underlying this estimate is not explained. The peculiar denominator is difficult to apply to real life. The risk for exposure during one year could be up to 50 times higher. It would be expressed more clearly as the number of cases per million defined daily doses (DDD), or per 100 000 packs sold.

Other analgesics significantly associated with agranulocytosis across regions were indomethacin (rr estimate 9) and the butazones (rr 4). Numbers were too small to allow estimation of rrs for other pyrazolones such as amidopyrine which is an acknowledged cause of agranulocytosis, or for other anti-inflammatory analgesics (NSAIDs) which are not. Use of salicylates or paracetamol was not associated with agranulocytosis or aplastic anaemia. These findings reinforce the arguments for banishing dipyrone[2] and where possible using paracetamol or aspirin instead.

The data on aplastic anaemia also bring some surprises. The overall annual incidence was 2·2 million, with a two-year fatality rate of 49%. Analgesic use by cases and controls in the period between six months and one month before hospital admission yielded rrs for individual drugs or groups of drugs. Histories of any exposure to indomethacin (rr 13), diclofenac (rr 9), and butazones (rr 9) were significantly associated with aplastic anaemia. For prolonged exposure to indomethacin or butazones the rate ratios were around four times higher; but these were based on small numbers. For the same reason, no rrs could be calculated for pyrazolones other than dipyrone, or for individual NSAIDs. The data thus do not incriminate other NSAIDs, but they raise the worrying suspicion that indomethacin, the butazones, and diclofenac may not be the only ones to carry a risk of aplastic anaemia. It certainly looks as if indomethacin ought to join phenylbutazone as a drug of last resort, but while data on the other NSAIDs are lacking it seems premature to regard diclofenac as a second-line drug.

This study is the first of its kind, and the courage and tenacity of the investigators in carrying it through despite some serious setbacks must be applauded. It confirms that dipyrone is a major cause of agranulocytosis and that phenylbutazone, indomethacin, and diclofenac can cause aplastic anaemia. It is now up to all of us—prescribers, drug regulators, and pharmaceutical companies—to use the results in the best interests of patients.

RESEARCH ON HEALTHY VOLUNTEERS

CONCERN about drug safety has led progressively to more stringent licensing requirements and more comprehensive investigation of drugs before they are marketed. As a result, more early phase trials are being conducted on healthy volunteers; the wheel has now turned full circle with two well-publicised reports of fatalities. The Medicines Commission responded by asking the Royal College of Physicians to set up a working party on research in healthy volunteers. In its report[1] the working party attempts to establish safeguards for such volunteers and recommends procedures for compensation in the event of harm.

Volunteer experiments are in danger of becoming big business. Several contract companies have been established to sell volunteer studies to pharmaceutical firms which lack the necessary in-house capacity. Such developments pose two important questions about those who carry out the work and those who volunteer to participate. Firstly, the facilities for early-phase studies have in some instances fallen well short of the ideal; in other cases, university or hospital staff have used the resources of their department as a sort of academic moonlighting. The report recommends that all premises should be open to scrutiny. A distinction is drawn between, on the one hand, NHS hospitals and university departments, which should be inspected "where necessary" by or on behalf of the local ethics committee, and, on the other hand, commercial institutions (including pharmaceutical companies) which "should" be subject to independent scrutiny. Further, a register of approved commercial institutions carrying out research on healthy volunteers is

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Table 4.—Agranulocytosis: Use of Dipyrone in the Week Before the Index Day According to Region

Region	No.* (%) of Cases	No.* (%) of Controls	Crude Rate Ratio Estimate†	Stratified Rate Ratio Estimate‡
Ulm, West Germany	6/28 (21)	5/237 (2)	12.7	12.2
West Berlin	6/17 (35)	2/72 (3)	19.1	20.9
Barcelona, Spain	15/50 (30)	5/394 (1)	33.3	30.5
Israel	13/65 (20)	28/253 (11)	2.0	1.8
Budapest, Hungary	4/30 (13)	22/147 (15)	0.9	0.9
Stockholm/Uppsala, Sweden	0/12 (0)	0/126 (0)	. . .	. . .
Milan, Italy	1/9 (11)	3/133 (2)	5.4	3.6
Sofia, Bulgaria	6/10 (60)	13/63 (21)	5.8	5.3
Total	51/221 (23)	78/1425 (6)	5.2	. . .

*Number of cases or controls who used dipyrone/total number in center.

†Relative to no use in the week before the index day.

‡Age and sex taken into account by the Mantel-Haenszel procedure. χ^2_3 for heterogeneity, 45.4; $P<.001$.

Table 5.—Agranulocytosis: Analgesic Use in the Week Before the Index Day

Drug	Cases (221)	Controls (1425)	Stratified Rate Ratio Estimate* (95% Confidence Interval)	Multivariate Rate Ratio Estimate* (95% Confidence Interval)
Dipyrone				
Ulm, West Germany/West Berlin/Barcelona, Spain				
Any	27	12	21.3 (11.7-38.9)	23.7 (8.7-64.4)
≥3 d	12	7	16.5 (7.2-38.0)	20.4 (5.6-74.1)
Israel/Budapest, Hungary				
Any	17	50	1.5 (0.8-2.7)	0.8 (0.4-1.8)
≥3 d	10	23	2.0 (0.9-4.4)	1.2 (0.4-3.7)
Other pyrazolones†				
Any	18	58	2.1 (1.2-3.7)	1.2 (0.6-2.5)
≥3 d	6	16	2.1 (0.8-5.4)	0.9 (0.2-3.1)
Salicylates				
Any	43	129	2.4 (1.6-3.6)	1.6 (1.0-2.7)
≥3 d	24	56	2.7 (1.6-4.6)	1.9 (1.0-3.8)
Acetaminophen				
Any	25	78	1.6 (1.0-2.6)	1.0 (0.5-1.9)
≥3 d	12	42	1.4 (0.7-2.9)	0.8 (0.3-2.0)
Butazones				
Any	11	11	5.2 (2.2-12.0)	3.8 (1.3-10.7)
≥3 d	8	6	6.7 (2.6-17.5)	6.3 (1.8-22.3)
Indomethacin				
Any	10	7	6.7 (2.8-16.1)	8.9 (2.9-27.8)
≥3 d	8	4	9.0 (3.2-25.4)	14.2 (3.7-54.4)
Other nonnarcotic analgesics‡				
Any	5	24	1.5 (0.5-4.0)	0.9 (0.3-3.1)
≥3 d	3	19	1.0 (0.3-3.7)	0.6 (0.1-2.6)

*Relative to no use in the week before the index day.

†Includes aminopyrine (six cases, 18 controls); aminopyrine/propyphenazone (five, 21); propyphenazone (three, seven); antipyrine (three, five); aminopyrine/propyphenazone plus propyphenazone (one, one); aminopyrine/propyphenazone plus antipyrine (zero, four); and propyphenazone plus antipyrine (zero, two). "Aminopyrine/propyphenazone" refers to compounds the components of which were changed from aminopyrine to propyphenazone during the course of this study.

‡Includes ibuprofen (two cases, four controls); diclofenac sodium (one, five); naproxen (one, three); proquazone plus piroxicam (one, zero); piroxicam (zero, three); benzydamine hydrochloride (zero, two); niflumic acid (zero, one); glafenine (zero, one); flurbiprofen (zero, one); ketoprofen (zero, one); clonixin (zero, one); naproxen plus diclofenac (zero, one); piroxicam plus diclofenac (zero, one).

terms for the use of thyrostatic drugs (propylthiouracil, carbimazole, and methimazole) and sulfonamides were included because these agents were associated, as expected, with agranulocytosis (thyrostatic drug use, 15% of cases and 0.4% of controls; sulfonamide use, 8% and 1%).

Excess risks were calculated using the multivariate rate ratio estimates. Since the estimates were based on drug histories covering seven days before the index day, excess risks were calculated for a seven-day period.

Specific Methods: Aplastic Anemia

The effects of drugs used up to 18[illegible] days before admission were assessed because there can be a considerable delay between exposure and diagnosis. Any use that took place less than 2[illegible] days previously was ignored, because such use could well have occurred after the onset of the dyscrasia. The reference category was no use of the drug under consideration during days 2[illegible] through 180 before admission. The distribution of analgesic use among the 1724 controls is given in Table 2; usage rates were reasonably similar.

The multiple logistic models included the following factors: age; sex; geographic area; date of interview; reliability of the patient; person interviewed; transfer from another hospital; histories of bruising, blood disorder, or tuberculosis; histories of exposure to benzene, petrochemicals, or insecticides; and the use of drugs during days 29 through 180 before admission (the drug groups were defined as for agranulocytosis). Thyrostatic drugs were used by 4% of the cases and 0.4% of the controls and sulfonamides by 10% and 4%; again, separate terms were included for these drugs.

As with agranulocytosis, excess risk calculations were based on the multivariate rate ratio estimates. Since these were based on drug histories covering days 29 through 180 before admission, excess risks were calculated for a five-month period.

RESULTS

Agranulocytosis

Table 3 gives estimated incidence rates by region. The overall annual incidence was 6.2 cases per million; it ranged from 1.7 per million in Milan to 9.0 per million in Budapest. Among the 422 cases, there were 36 deaths for which agranulocytosis was the main contributory cause, giving a fatality rate of 9% and an annual mortality rate of 0.5 per million.

The annual community incidence

Examples of apparent deception or lack of frankness listed under category 4 touch the very heart of the demand for full disclosure. Yet I believe most doctors would take the view that patients should not be burdened with a serious diagnosis which is merely probable or possible, if it does not affect the current management.

Those in favour of patients' having access to their medical records argue that seeing these documents is in most instances reassuring. I estimate that this would have been so in approximately a third of the cases in the present series. There is some evidence that reading the specialist's advice to stop smoking is more effective than merely hearing it. These beneficial effects would, however, be appreciably reduced once patients knew that the doctor realised that they would be likely to read what he had written.

It is widely, though not universally, held that some medical records contain information which should, in the patient's own interests, not be accessible. What is not sufficiently appreciated is the high proportion of records to which this reservation applies—at least in some specialties. In the present sample, 42 out of 100 sets of notes contained at least one comment likely to give rise to alarm or anxiety—an effect which might persist despite explanation and reassurance.

Open access to medical records would profoundly affect the specialist's system of note-keeping. Besides having to develop a plan for avoiding ambiguous or potentially worrying symbols, he would be compelled to alter his hitherto frank style. Where alarming or objectionable statements could not be avoided, he would undoubtedly find some way of keeping a second set of notes. Sensitive material would be communicated to the GP verbally instead of being committed to writing, with the danger that it would be forgotten or attached to the wrong patient.

Correcting misunderstandings and allaying fears fostered by reading raw data couched in technical language would also take more of the consultant's (and presumably the general practitioner's) time. There would undoubtedly be a major increase in cost to the NHS, both in paying for the additional medical time and in arranging for the notes to be made available to the patients under supervision. There would also be a danger of defacement or loss.

The fundamental question is: What is best for the patient? Medical science exists primarily for patients, not for doctors. The answer surely is that the patient needs to have all the information which would enable him or her to preserve or restore his health to the maximum degree possible, and to discharge his duties to his family and to society. The patient should not be presented with information which is likely to have the opposite effect.

CONCLUSION

I can appreciate that patients and potential patients want to take greater responsibility for their own health, and they want to have all the information available to enable them to do this. This is right. They know that doctors sometimes fail to provide them with important information and may make inaccurate entries in their medical records. This is true. They think that by insisting on seeing their records they would avoid these problems. This is a mistake. Patients would be overloaded with information, which their doctor would need to explain—if he had time. More seriously, the notes and letters in the record available to the patient would cease to be frank.

What is needed is better record keeping and more time spent in consultation with the patient; improved communication in the traditional manner, rather than open access to medical records. The findings of this small study support the view that access to personal health data should be limited to the disclosure of bare administrative details, such as whether the inquirer is on a waiting list, and the name of the consultant. Any patient who wanted to pursue the matter further could then approach the consultant for more detailed information.

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Drugs and the Third World

DRUG MARKETING IN THE THIRD WORLD: BENEATH THE COSMETIC REFORMS

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ELEVEN years ago Silverman and Lee, in *Pills, Profits and Politics*, drew attention to the unethical marketing tactics of certain US-based drug companies in Latin America.[1] Four years ago Dianna Melrose, in the controversial *Bitter Pills*, claimed that western multinational companies continued to make fat profits from the "dumping" of harmful and therapeutically useless drugs throughout the Third World.[2] These and other books have had impact, and standards of drug marketing, as many would measure them, have risen. However, from what I found during the four months that I spent in India recently conducting a field study into the prescribing practices of rural medical practitioners[3] the reforms in the drug industry seem to have been a pyrrhic victory.

In India I introduced myself as "a foreign doctor interested in diseases in this area" and followed 2400 patients through medical consultations. I recorded for each patient the presenting complaint, the stated clinical findings, and the drugs prescribed. In addition, I collected promotional literature from medical journals and drug company representatives, and sat in on interviews between the representatives and local doctors.

Examples of inexcusable marketing behaviour by western-based companies can still be found. Merck (India), in an advertisement that names Merck, Darmstadt, West Germany, as its parent company, promotes 'Encephabol' (pyritinol, a vitamin B_6 derivative) as a brain tonic that "improves the uptake and utilisation of glucose in the brain", and recommends its use for "strokes, organic brain syndrome of the elderly, post concussion syndrome, perinatal distress . . . (and) learning disorders".[4] I saw only two qualified doctors prescribe this drug—in both instances for a complaint of "weakness"—but I noted its unrestricted sale over the counter in street pharmacies and bought it

myself from a market stall. Parke-Davis were still promoting the anabolic steroid 'Adroyd' (oxymetholone) for "underweight or asthenic patients, convalescence from acute infectious diseases, . . . chronic debilitating illness, osteoporosis, fractures, . . . (and) decubitus ulcers".[4] I saw this product prescribed by doctors for complaints of weakness, sore throat, and fever.

Such aggressive promotion of useless and dangerous drugs is indefensible, but I believe it is diminishing. Only a handful of western companies are still prepared to risk their reputations in this way. However, this practice is being replaced by a subtler one, whose effects are more insidious, more widespread, and at least as dangerous—namely, the inappropriate prescription of drugs which are useful (even essential) in certain circumstances but contraindicated in others.

Take the prescription of analgesics, for example. The analgesic amidopyrine, its sodium sulphonate dipyrone (analgin), and the anti-inflammatory drugs phenylbutazone and oxyphenbutazone made up the majority of both general practitioner prescriptions and over-the-counter sales of analgesics in my study. Despite warnings on package inserts of the risk of fatal blood dyscrasias, one or more of these drugs were given to over 50% of patients requesting an analgesic. European-based multinationals, including Hoechst, Evans, Concept, Merck, and Glaxo (India), all obtain considerable revenue from wide sales of these "second line drugs", even though (a cynic would say because) their use has been severely restricted in the West.[5,6]

Chloramphenicol, whose use in the West is similarly restricted, accounted for 11% of all antimicrobial prescriptions in my study and was the commonest antimicrobial sold without a prescription. Although package inserts warning of the danger of aplastic anaemia were supplied with each bottle, the practical reality was, at best, that of a general practitioner counting out loose tablets into an envelope and, at worst, that of a pharmacist selling them over the counter one or two at a time from an opened bottle. One pharmacist, commended me on my interest in the package insert he was about to discard and explained, "This is legislation. Government now approve to this drug".

High-dose oestrogen-progesterone combination preparations have repeatedly been shown to be teratogenic;[7,8] in India they are allowed to be sold specifically for dysfunctional uterine bleeding. Package inserts warn that they should not be used in pregnancy. Yet they continued to be prescribed as the cheapest and most widely available pregnancy test in the country (I never saw it prescribed for anything else), and I was sold the drug at each of ten pharmacies where I requested a pregnancy test.

A final example is the use of nutritional substitutes. 40 000 children in India still go blind every year because the government cannot afford to fund a systematic programme of vitamin A supplementation; yet over a quarter of the country's total drugs bill is spent on the erratic and indiscriminate sale of vitamin and mineral supplements. 729 such products are listed in the *Indian Pharmaceutical Guide*, and they form the most commonly prescribed class of drug in all the areas I visited, accounting for 23% of all drugs dispensed. General practitioners prescribed them for over half of all patients, and many declared their belief that prescribed nutritional supplements were essential for health. No-one can make a case for the banning of vitamin syrups in a country where 90% of the children are at least mildly malnourished, but to see vitamins in an expensive form prescribed for children with the marasmus of raw poverty begs the question: who takes responsibility for their sales?

Phenylbutazone, chloramphenicol, and vitamin supplements are useful and appropriate drugs in the right clinical context. I prescribe them myself. And tighter indications and sterner warnings are now being provided (ostensibly) to restrict their use. But the reality is that these drugs continue to be used for trivial and bizarre indications by doctors who have no real grasp of their dangers and limitations.

Of the 26 general practitioners I interviewed not one took seriously the possibility of fatal side-effects with amidopyrine derivatives or chloramphenicol. Doctors held the attitude that "if I prescribe it 30 times a day, and it is freely available over the counter, it must be safe".

This attitude cannot be condoned, but it occurs in a context where it cannot easily be condemned. The vast majority of rural doctors work in conditions of extreme material hardship and professional isolation. There is no peer review, no clinical feedback, no system for reporting or investigating adverse drug reactions, and no access to independent information on the drugs they prescribe. Postgraduate education in clinical pharmacology is, for the rural doctor, the unchallenged province of representatives from the pharmaceutical industry. Many representatives are paid only by commission on the drugs they sell. The free samples and financial incentives they liberally offer seem to be highly effective in areas where the doctors themselves are living well below the poverty line. The representatives are, in general, poorly informed of the indications for their products, and often uninformed of serious side-effects. Their sales techniques are simple—they generally show colour charts bearing pictures of the drug and a list of indications in bold print. A flash-card from Glaxo (India) states that "In DEBILITY and GENERAL WEAKNESS, associated with tuberculosis, diabetes, liver disease, cardiac disease, BECADEXAMIN (a multivitamin/mineral supplement) helps healing, promotes growth, restores taste, replenishes deficiencies". The verbal claims made by the representatives surpass even such wide-ranging printed texts, and the combination of eastern enthusiasm with personal financial incentive adds a disturbing sincerity to their affirmations. Far from being disdained by the doctors, company representatives are welcomed with great ceremony as friends and fellow professionals in an otherwise lonely subculture. I got the impression that companies gained more sales through this curious camaraderie than through any form of "promotion" in the narrower sense.

In conclusion, the success of local and international pressure groups in persuading multinational drug companies to produce responsible advertisements and comprehensive package inserts has been a pyrrhic victory indeed. For some companies, the responsibility which began with the package insert ends there, and their directors have used the indications for which a drug is now recommended as an official excuse for ignoring the situations in which it is actually used. Cleverly worded small print (in a language which most of the

patients do not speak) provides the multinational company with legal immunity and transfers the moral accountability for drug deaths onto the poorly-informed and professionally isolated Third World doctor, while the dubious backstage behaviour of the company representative is quietly ignored.

I have watched, in the slums of Calcutta, a young mother spend two days' wages on 'Orabolin' drops (ethyloestrenol, an anabolic steroid), and feed the whole bottle to marasmic twins through a rusty teaspoon. She could not read a word of the warnings on the package insert which I bought off her for a rupee, but she responded to the picture of the healthy baby on the box. Official legislation rarely can and almost never does change realities such as these. India already has so many cumbersome laws on the prescription and dispensing of drugs that the government's hands are consistently tied by its own red tape and the administrative infrastructure is pitiably inadequate for carrying out the volumes of official instructions. I hope that I have shown that the focus of reform must shift from the nitpicking of legal loopholes to the reality of what is actually being prescribed and dispensed, to whom and for what.

In Britain, no case of drug damage has gone as far as settlement in a court of law. Thalidomide was not banned—it was voluntarily withdrawn following a public outcry. It is time for another public outcry. It is time the World Health Organisation gave financial and scientific support for the continued education and updating of Third World doctors in the difficult and ever-changing subject of clinical pharmacology. It is time the multinational drug industry stopped trumping its ethical responsibilities with its commercial obligations. And it is time the British Medical Association had the courage to use its professional power to demand that British-based drug companies be morally accountable for the deaths their drugs have caused in the Third World.

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Hospital Practice

THE FIVE-YEAR BURP SYNDROME

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THERE is no argument about the cyclical nature of many biological phenomena, such as sleep, ovulation, and hibernation; that the higher functions of human beings are also subject to cycles is, however, less evident—though well accredited, for instance, in the manic-depressive psychoses and in schizophrenic episodes. The somewhat fanciful urge for a periodic change of sexual partner is, of course, the basis for *The Seven Year Itch*, the 1950s film featuring Marilyn Monroe at her best. Many years' experience of the same hospital outpatient clientele suggests that psychoneurotic symptoms may also run in cycles. It is a commonplace that neurotic patients may change the focus of illness from one organ system to another with bewildering frequency. For the purposes of this paper, however, I have selected patients with recurrent gastrointestinal upsets in which the most common symptoms are burping and the distension and discomfort that proceed from this habit. Just a few of the patients included have had recurrent cardiopulmonary symptoms such as chest pain and overbreathing; their inclusion emphasises that the syndrome described here is not after all specific to any body system and that specialists in other fields will be perfectly well acquainted with it.

THE PATIENTS

The patients studied were attending the London Hospital outpatients department for the second time, at least two years after the initial investigation. All were still complaining of their initial symptoms, for which no organic cause was evident. Patients reporting initially to another hospital and then coming to the London Hospital for a second opinion are not included. 43 patients (25 women, 18 men) are considered, 35 being in the fourth to sixth decades of life at the time of their first visit. Between them the patients paid 109 visits to the outpatient clinic, 4 of them contributing four visits each for the same symptoms at approximately 5-year intervals. The table shows that 5 years was in fact the mode and also, by elementary calculation, the mean interval between visits.

DISTRIBUTION OF INTERVALS BETWEEN OUTPATIENT VISITS

Years between outpatient visits	2	3	4	5	6	7	8	9	10	11	12	13	14	15
No of repeat visits	7	4	9	19	14	5	0	2	3	1	0	1	0	1

That the frequency of outpatient attendances was not due to the whim of a small number of general practitioners is attested by the fact that 46 GPs were involved and only 4 referred a patient more than once; it could, therefore, be argued that subsequent referrals were more often due to a change in general practitioner, though in most cases this was another member of the same practice partnership.

DISCUSSION

What appears to the hospital clinician as a cyclical phenomenon may be less evident as such to the referring general practitioner, who in most cases will be aware that his patient is prone to neurotic complaints. The common story seems to be that following the first hospital investigation reassurance so gained lasts for 2-3 years before confidence wanes and symptoms become less tolerable. Many patients have the experience of a relative or friend being assured that his or her symptoms were due to "nerves", only to die of cancer soon afterwards. Or the patient may express the feeling that symptoms "have gone on so long that surely something (meaning cancer) might develop".

The conscientious general practitioner will try reassurance and symptomatic remedies for a further year or so and then, yielding to pressure from patient or relatives and perhaps with the feeling that 5 years is a decent interval, refer the patient again. On the hospital side it is important to recognise that such patients need explanation of their symptoms and support, not reinvestigation.

Risks of Agranulocytosis and Aplastic Anemia

A First Report of Their Relation to Drug Use With Special Reference to Analgesics

The International Agranulocytosis and Aplastic Anemia Study

The risks of agranulocytosis and aplastic anemia in relation to analgesic drug use were evaluated in a population-based case-control study conducted in Europe and Israel. Analgesic use in the week before the onset of illness was compared between 221 cases of agranulocytosis and 1425 hospital controls. Analgesics significantly associated with agranulocytosis were dipyrone (metamizol sodium), indomethacin, and butazones (phenylbutazone and oxyphenbutazone). For dipyrone, the rate ratio estimate was 23.7 in Ulm, West Germany, West Berlin, and Barcelona, Spain, and the estimated excess risk for any exposure in a one-week period was 1.1 per million. In Israel and Budapest, Hungary, where the rate ratio estimate was 0.8, there was no evidence of excess risk. In all of the regions combined, the rate ratio estimates were 8.9 for indomethacin and 3.8 for butazones, with excess risk estimates of 0.6 and 0.2 per million, respectively. Analgesic use 29 to 180 days before admission was compared between 113 cases of aplastic anemia and 1724 controls. Indomethacin (rate ratio estimate, 12.7), diclofenac sodium (8.8), and butazones (8.7) were significantly associated with aplastic anemia, with estimated excess risks for any exposure in a five-month period of 10.1, 6.8, and 6.6 per million, respectively.

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AGRANULOCYTOSIS and aplastic anemia are rare diseases that can be caused by many environmental factors, including a variety of drugs.[1-4] There are, however, no reasonably accurate estimates of the overall incidence of either disease or of the risk associated

See also p 1788.

with any particular exposure, and regulations concerning the various suspect agents vary from one country to another. In view of this situation, the present international case-control study was undertaken to obtain quantitative estimates of the incidence of the two diseases and the magnitude of the risks in relation to various agents, particularly drugs.

The study is continuing in several countries, but enough data have already been obtained to enable us to report on the overall incidence of each disease and on the risks associated with the use of analgesics.

METHODS

This population-based case-control study[5] was originally organized in Israel (population, 3.9 million), Barcelona, Spain (4.1), Ulm, West Germany (5.3), West Berlin (1.8), and Milan, Italy (2.3). After a pilot phase, data collection began on July 1, 1980. Three additional regions joined subsequently: Budapest, Hungary (2.0 million), in December 1981, Sofia, Bulgaria (1.1), in August 1982, and Stockholm/Uppsala, Sweden (1.8), in January 1983.

Efforts were made to identify all cases of agranulocytosis and aplastic anemia that resulted in hospital admission (community cases) or that occurred during a hospital stay (hospital cases). To ascertain potential cases, study centers maintained regular liaison with all hospitals in the regions at intervals of no more than two weeks. The present report is based on cases identified up to June 30, 1984.

Potential controls for community cases of both agranulocytosis and aplastic anemia were selected from among other patients admitted to the same hospitals at about the same time, who were of the same sex and approximately the same ages as the cases.

The controls for the hospital cases were to have been a random sample of all hospital patients[6] who were not receiving cancer chemotherapy, immunotherapy, or radiotherapy. In practice, such a sample could not be obtained, principally because patients with serious illnesses frequently were inaccessible for interview. Therefore, hospital cases were not included in the analysis of the effects of drug use.

Specially trained nurses or physicians administered a standard questionnaire to potential cases and controls. For young children, a parent or guardian was interviewed. Detailed information was obtained about drug use, day by day for the first seven days before admission, week by week for the three weeks before that, anytime in the five months before that, and anytime in the more distant past.

To ensure that drug histories were as complete as possible, patients were first asked about indications. With regard to analgesics, they were questioned about use for pain, headache, backache, toothache, menstrual cramps, muscle relaxation, muscle

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Table 1.—Agranulocytosis: Use of Analgesics by 1425 Controls in the Week Before the Index Day* According to Diagnosis

Drug	Diagnostic Category, No. (%)†		
	Trauma (N=787)	Infection (N=396)	Other (N=242)
Dipyrone	35 (5)	27 (6)	16 (5)
Other pyrazolones‡	29 (4)	21 (6)	8 (3)
Salicylates	67 (8)	42 (10)	20 (7)
Acetaminophen	34 (4)	25 (7)	19 (8)
Butazones	6 (1)	3 (1)	2 (1)
Indomethacin	4 (0.4)	1 (0.2)	2 (0.4)
Other nonnarcotic analgesics	16 (2)	3 (1)	5 (2)

*Two hundred ninety-nine controls for whom the index day was unknown are excluded.
†Standardized to the overall age, sex, and geographic distribution of the control series.
‡Aminopyrine, antipyrine, and propyphenazone.

spasms, arthritis, gout, cough, colds, influenza, and other infections. A list of generic and trade names was then read. The list was based on marketing data for each region and included names that together accounted for over 90% of the sales of the common nonnarcotic analgesic drugs (there were too many trade names to ask about the remaining 10%) as well as other drugs generally suspected of causing either dyscrasia. To minimize memory loss further, patients were not interviewed if they had been in the hospital more than 28 days.

Data collected on potential confounding factors included, in addition to medication histories, demographic information such as age and years of education, medical information such as major illnesses and history of allergy, and limited information on exposure to radiation, petrochemicals, laboratory chemicals, insecticides, and benzene.

Information on the clinical course of the illness was recorded for all subjects (for agranulocytosis, this included systematic questions on the time of onset of sore throat, fever, and chills). In addition, for all cases (including those not interviewed), blood smears, bone marrow aspirates, and biopsy sections were obtained, whenever available. All available blood cell counts were recorded, together with other relevant clinical and laboratory information.

Definition and Selection of Cases of Agranulocytosis

Potential cases were patients with a granulocyte count of 500/mm^3 or less ($\leq 0.5\times10^9$/L) or a total white blood cell count of 3000/mm^3 or less ($\leq 3.0\times10^9$/L) who were not undergoing cancer chemotherapy, radiation therapy, or immunosuppressive therapy. A lower age limit of 2 years was specified because transient neutropenia in younger children is commonly associated with viral infections.[7] There was no upper age limit. The diagnoses of potential cases were confirmed by a committee of hematologists, who examined the clinical and laboratory data, including peripheral blood smears, bone marrow aspirates, and biopsy specimens. The review was carried out without knowledge of drug use.

Final cases were patients with severe selective neutropenia, defined as a granulocyte count of 500/mm^3 or less ($\leq 0.5\times10^9$/L) with a hemoglobin level of 10 g/dL or greater ($\geq$100 g/L) and a platelet count of 100 000/mm^3 or greater ($\geq 100\times10^9$/L). Patients with systemic diseases that can be associated with neutropenia (eg, infectious mononucleosis, systemic lupus erythematosus, leukemia, and malignant lymphoma) were excluded. If a bone marrow aspirate or biopsy specimen was not available, the diagnosis was accepted if the neutrophil count returned to normal within 30 days (105 cases). There were 422 final cases, of which 300 were community cases and 122 were hospital cases.

Because the major symptoms of agranulocytosis—sore throat, fever, chills, and headache—could each have prompted the use of analgesic drugs, there was a particular need for careful timing of the day of clinical onset (index day) of the illness, without knowledge of drug use. The index day was deemed to be the day on which sore throat, fever, or chills first occurred, as reported by the patient.

Of the 300 community cases, 47 (16%) were not interviewed for the following reasons: death (7%), a delay of more than 28 days (5%), psychological or medical reasons (3%), and failure to locate the patient (0.3%). Among the remaining 253 cases, there were six refusals (2%) and 39 (15%) for whom the index day could not be determined, leaving 208. Finally, 13 pilot cases with an identifiable index day were also included in the analysis of drug use, giving a total of 221.

Definition and Selection of Cases of Aplastic Anemia

Potential cases of aplastic anemia were patients who were not undergoing cancer chemotherapy, radiation therapy, or immunosuppressive therapy and who met at least two of the following criteria: a white blood cell count of 3500/mm^3 or less ($\leq 3.5\times10^9$/L), platelet count of 50 000/mm^3 or less ($\leq 50\times10^9$/L), or hemoglobin value of 10.0 g/dL or less ($\leq$100 g/L) with a reticulocyte count of 30 000/mm^3 or less ($\leq 30\times10^9$/L). As with agranulocytosis, the diagnoses of potential cases were confirmed, without knowledge of drug use, by the committee of hematologists.

Final accepted cases were patients who did not have neoplastic or granulomatous disease involving the bone marrow, systemic lupus erythematosus, hypersplenism, or other conditions masquerading as aplastic anemia. The bone marrow biopsy specimen, if available, had to be compatible with the diagnosis. In the absence of a biopsy specimen, the diagnosis was accepted if there were at least two typical marrow aspirates and if the clinical presentation and progression were typical (nine cases). There were 168 final cases, of which 160 were community cases and eight were hospital cases.

Because the presenting symptoms of aplastic anemia (eg, fatigue or excessive bruising) are too vague to be timed with acceptable precision, it was not possible to determine the date of onset (index day).

Of the 160 community cases, 53 (33%) were not interviewed for the following reasons: a delay of more than 28 days (22%), death (8%), psychological or medical reasons (1%), failure to locate the patient (0.6%), and language difficulties (0.6%). The remaining 16 were combined with five pilot cases, giving a total of 113 cases included in the analysis of drug use.

Definition and Selection of Controls

There were 2408 potential controls. Of these, 27 (1%) refused to be interviewed. The selection of final controls from the remaining 2381 was made without knowledge of drug use. Two categories were considered eligible:

first was patients with acute conditions not known to be caused, prevented by, or otherwise associated with analgesic use (eg, trauma and acute infections); these conditions were judged to be independent of analgesic use prior to their onset. The second category consisted of patients admitted electively for long-standing conditions thought not to influence analgesic use (eg, hernia); these conditions were judged to be independent of analgesic use prior to the date of admission. There were 1724 eligible controls.

In analyzing agranulocytosis, the control series was further restricted to those with a known index day (as with the case series): for those with trauma, this was the day on which the accident occurred; for those with other acute conditions (such as infections), it was the day on which symptoms commenced; and for those admitted with chronic conditions, it was the day of admission. The index day could be determined for 1425 patients. Thus, the final comparison involved 221 cases of agranulocytosis and 1425 controls.

In analyzing aplastic anemia, the control series was not restricted because an index day was not specified. Thus, the final comparison involved 113 cases and 1724 controls.

Data Analysis

Rate ratios for various categories of drug exposure were estimated from stratified data using the Mantel-Haenszel method,[8] and 95% confidence intervals were calculated according to the method of Miettinen.[9] The stratification variables were age (<40, 40 to 59, 60 to 69, and ≥70 years), sex, and region. To control simultaneously all identified potential confounding factors, rate ratios were also estimated by multiple logistic regression,[10] using somewhat different models for each dyscrasia (see below).

The most recent census data were used to estimate the incidence of the two dyscrasias. Then, for each drug at issue, the excess risk was estimated as follows: the etiologic fraction (that proportion of the disease attributable to use of the drug) was calculated[11]; the latter estimate, together with the rate ratio estimate and incidence rate, was used to calculate risk estimates for users and nonusers[5]; the excess risk was the difference between the two estimates.[5]

Specific Methods: Agranulocytosis

The effects of drug use in the seven days before the index day were assessed, because drug-induced agranulocytosis is frequently characterized by a short induction period.[3] Use that took place on or after the index day or more than a week previously was ignored. The reference category consisted of those not exposed to the drug under consideration in the week before the index day. The control distribution of analgesic use according to three diagnostic categories is given in Table 1. The rates of use were relatively low and there was some variation across diagnosis, but in general the rates were similar.

The following factors were included in the multivariate models: age; sex; geographic area; date of interview; reliability of the patient (as assessed by the interviewer); person interviewed (patient, parent, or guardian); transfer from another hospital; histories of allergy, blood disorder, blood transfusion, or infectious mononucleosis; exposure to insecticides; the use in the week before the index day of dipyrone, other pyrazolones, salicylates, acetaminophen, indomethacin, butazones (phenylbutazone and oxyphenbutazone), other nonnarcotic analgesics, thyrostatic drugs, sulfonamides, a combined category of other drugs generally suspected as causes of agranulocytosis (eg, phenothiazines and gold); and, finally, the use of any nonsuspect drugs. Separate

Table 2.—Aplastic Anemia: Use of Analgesics by 1724 Controls in Days 29 to 180 Before Admission According to Diagnosis

Drug	Diagnostic Category, No. (%)*		
	Trauma (N=796)	Infection (N=579)	Other (N=349)
Dipyrone	130 (20)	179 (24)	109 (26)
Other pyrazolones†	154 (19)	124 (22)	77 (26)
Salicylates	378 (45)	295 (52)	150 (40)
Acetaminophen	143 (23)	156 (22)	82 (20)
Butazones	19 (2)	9 (2)	12 (3)
Indomethacin	10 (1)	4 (1)	4 (1)
Diclofenac	7 (0.7)	4 (0.6)	6 (1.9)
Other nonnarcotic analgesics	29 (3)	8 (2)	8 (2)

*Standardized to the overall age, sex, and geographic distribution of the control series.
†Aminopyrine, antipyrine, and propyphenazone.

Table 3.—Agranulocytosis: Annual Incidence Rates According to Region, July 1980 to June 1984

Region	Population, Millions	Interval, mo	Community Cases		No. of Hospital Cases	Total	
			No.	Rate/Million/y*		No.	Rate/Million/y*
Ulm, West Germany	5.3	48	67	3.5	55	122	6.3
West Berlin	1.8	48	21	2.3	17	38	4.6
Barcelona, Spain	4.1	48	62	4.2	23	85	5.7
Israel	3.9	48	64	5.6	12	76	6.5
Budapest, Hungary	2.0	31†	42	7.2	10	52	9.0
Stockholm/Uppsala, Sweden	1.8	18‡	19	7.0	3	22	8.0
Milan, Italy	2.3	45§	13	1.5	2	15	1.7
Sofia, Bulgaria	1.1	23‖	12	5.4	0	12	5.4
Total	22.3	...	...	4.4¶	...	...	6.2¶

*Standardized to the age and sex distribution of the study population.
†December 1981 to June 1984.
‡January 1983 to June 1984.
§October 1980 to June 1984.
‖August 1982 to June 1984.
¶Calculated as a population-weighted average of the age- and sex-standardized region-specific rates.

Table 4.—Agranulocytosis: Use of Dipyrone in the Week Before the Index Day According to Region

Region	No.* (%) of Cases	No.* (%) of Controls	Crude Rate Ratio Estimate†	Stratified Rate Ratio Estimate‡
Ulm, West Germany	6/28 (21)	5/237 (2)	12.7	12.2
West Berlin	6/17 (35)	2/72 (3)	19.1	20.9
Barcelona, Spain	15/50 (30)	5/394 (1)	33.3	30.5
Israel	13/65 (20)	28/253 (11)	2.0	1.8
Budapest, Hungary	4/30 (13)	22/147 (15)	0.9	0.9
Stockholm/Uppsala, Sweden	0/12 (0)	0/126 (0)	. . .	. . .
Milan, Italy	1/9 (11)	3/133 (2)	5.4	3.6
Sofia, Bulgaria	6/10 (60)	13/63 (21)	5.8	5.3
Total	51/221 (23)	78/1425 (6)	5.2	. . .

*Number of cases or controls who used dipyrone/total number in center.

†Relative to no use in the week before the index day.

‡Age and sex taken into account by the Mantel-Haenszel procedure. χ^2_6 for heterogeneity, 45.4; $P<.001$.

Table 5.—Agranulocytosis: Analgesic Use in the Week Before the Index Day

Drug	Cases (221)	Controls (1425)	Stratified Rate Ratio Estimate* (95% Confidence Interval)	Multivariate Rate Ratio Estimate* (95% Confidence Interval)
Dipyrone				
Ulm, West Germany/West Berlin/Barcelona, Spain				
Any	27	12	21.3 (11.7-38.9)	23.7 (8.7-64.4)
≥3 d	12	7	16.5 (7.2-38.0)	20.4 (5.6-74.1)
Israel/Budapest, Hungary				
Any	17	50	1.5 (0.8-2.7)	0.8 (0.4-1.8)
≥3 d	10	23	2.0 (0.9-4.4)	1.2 (0.4-3.7)
Other pyrazolones†				
Any	18	58	2.1 (1.2-3.7)	1.2 (0.6-2.5)
≥3 d	6	16	2.1 (0.8-5.4)	0.9 (0.2-3.1)
Salicylates				
Any	43	129	2.4 (1.6-3.6)	1.6 (1.0-2.7)
≥3 d	24	56	2.7 (1.6-4.6)	1.9 (1.0-3.8)
Acetaminophen				
Any	25	78	1.6 (1.0-2.6)	1.0 (0.5-1.9)
≥3 d	12	42	1.4 (0.7-2.9)	0.8 (0.3-2.0)
Butazones				
Any	11	11	5.2 (2.2-12.0)	3.8 (1.3-10.7)
≥3 d	8	6	6.7 (2.6-17.5)	6.3 (1.8-22.3)
Indomethacin				
Any	10	7	6.7 (2.8-16.1)	8.9 (2.9-27.8)
≥3 d	8	4	9.0 (3.2-25.4)	14.2 (3.7-54.4)
Other nonnarcotic analgesics‡				
Any	5	24	1.5 (0.5-4.0)	0.9 (0.3-3.1)
≥3 d	3	19	1.0 (0.3-3.7)	0.6 (0.1-2.6)

*Relative to no use in the week before the index day.

†Includes aminopyrine (six cases, 18 controls); aminopyrine/propyphenazone (five, 21); propyphenazone (three, seven); antipyrine (three, five); aminopyrine/propyphenazone plus propyphenazone (one, one); aminopyrine/propyphenazone plus antipyrine (zero, four); and propyphenazone plus antipyrine (zero, two). "Aminopyrine/propyphenazone" refers to compounds the components of which were changed from aminopyrine to propyphenazone during the course of this study.

‡Includes ibuprofen (two cases, four controls); diclofenac sodium (one, five); naproxen (one, three); proquazone plus piroxicam (one, zero); piroxicam (zero, three); benzydamine hydrochloride (zero, two); niflumic acid (zero, one); glafenine (zero, one); flurbiprofen (zero, one); ketoprofen (zero, one); clonixin (zero, one); naproxen plus diclofenac (zero, one); piroxicam plus diclofenac (zero, one).

terms for the use of thyrostatic drugs (propylthiouracil, carbimazole, and methimazole) and sulfonamides were included because these agents were associated, as expected, with agranulocytosis (thyrostatic drug use, 15% of cases and 0.4% of controls; sulfonamide use, 8% and 1%).

Excess risks were calculated using the multivariate rate ratio estimates. Since the estimates were based on drug histories covering seven days before the index day, excess risks were calculated for a seven-day period.

Specific Methods: Aplastic Anemia

The effects of drugs used up to 180 days before admission were assessed because there can be a considerable delay between exposure and diagnosis. Any use that took place less than 29 days previously was ignored, because such use could well have occurred after the onset of the dyscrasia. The reference category was no use of the drug under consideration during days 29 through 180 before admission. The distribution of analgesic use among the 1724 controls is given in Table 2; usage rates were reasonably similar.

The multiple logistic models included the following factors: age; sex; geographic area; date of interview; reliability of the patient; person interviewed; transfer from another hospital; histories of bruising, blood disorder, or tuberculosis; histories of exposure to benzene, petrochemicals, or insecticides; and the use of drugs during days 29 through 180 before admission (the drug groups were defined as for agranulocytosis). Thyrostatic drugs were used by 4% of the cases and 0.4% of the controls and sulfonamides by 10% and 4%; again, separate terms were included for these drugs.

As with agranulocytosis, excess risk calculations were based on the multivariate rate ratio estimates. Since these were based on drug histories covering days 29 through 180 before admission, excess risks were calculated for a five-month period.

RESULTS

Agranulocytosis

Table 3 gives estimated incidence rates by region. The overall annual incidence was 6.2 cases per million; it ranged from 1.7 per million in Milan to 9.0 per million in Budapest. Among the 422 cases, there were 36 deaths for which agranulocytosis was the main or contributory cause, giving a fatality rate of 9% and an annual mortality rate of 0.5 per million.

The annual community incidence

was 4.4 per million. Among the 300 community cases there were 29 deaths (fatality rate, 10%; mortality, 0.4 per million). The hospital incidence could not be estimated because the denominator (the number of person-years of bed occupancy) was not known; among the 122 hospital cases, there were seven deaths (6%).

Preliminary analysis revealed that there was significant regional variability ($P<.001$) in the rate ratio estimate for the use of dipyrone (Table 4). Whereas the crude rate ratio estimate for all regions was 5.2, the region-specific estimates ranged from 0.9 in Budapest to 33.3 in Barcelona. Adjustment for age and sex did not change the estimates materially.

In the separate regions, numbers were too small to control confounding from factors other than age and sex. Therefore, to provide stable multivariate estimates, the data were grouped in categories of high rate ratio (Ulm, Berlin, and Barcelona) and low rate ratio (Israel and Budapest). Results for these categories are presented separately. It was not clear how to categorize the data from Milan and Sofia, and further data on dipyrone from these two regions are not presented.

Regional heterogeneity in the rate ratio estimate was not evident for any other analgesic drug, although in each region numbers for most drugs were small. Overall results are therefore presented for analgesics other than dipyrone.

In Table 5 two categories of analgesic use in the week before the index day—any use and use for at least three consecutive days—are given for cases and controls. In Ulm, Berlin, and Barcelona, the multivariate rate ratio estimate for any dipyrone use was 23.7 (95% confidence interval, 8.7 to 64.4); in Israel and Budapest it was 0.8 (0.4 to 1.8). In all regions combined, other analgesics significantly associated with agranulocytosis were indomethacin (multivariate rate ratio estimate, 8.9) and butazones (3.8). For any salicylate use the estimate was 1.6 (lower 95% confidence limit, 1.0). The estimates for pyrazolones other than dipyrone (1.2), acetaminophen (1.0), and other nonnarcotic analgesics as a group (0.9) were all close to unity. Individual drugs in the categories of other pyrazolones and other nonnarcotic analgesics could not be evaluated because of small numbers. When the analysis was restricted to use that took place on at least three consecutive days, none of the rate ratio estimates was materially reduced.

In earlier studies[12,13] the risk associated with the use of pyrazolones for 14 or more days was reported. In this study, in Ulm, Berlin, and Barcelona only one case and five controls who had used dipyrone within one week of the index day had taken the drug for 14 or more consecutive days; in Israel and Budapest the corresponding numbers were five and ten (multivariate rate ratio estimate, 2.2; 95% confidence interval, 0.5 to 10.4). With regard to other drugs, there were sufficient data to examine 14 or more consecutive days of use only for salicylates: there were 12 exposed cases and 24 exposed controls (multivariate rate ratio estimate, 2.9; 95% confidence interval, 1.2 to 7.1).

Estimates of excess risk were calculated for those analgesics (dipyrone, butazones, and indomethacin) for which the lower 95% confidence limit, based on a history of any use in the week before the index day, was greater than 1.0. For dipyrone use in Ulm, Berlin, and Barcelona, the estimated etiologic fraction was 27%, which translated into an excess risk of 1.1 per million. For butazone use in all regions combined, the etiologic fraction was 4%, giving an excess risk estimate of 0.2 per million. For indomethacin use, the etiologic fraction and excess risk were 4% and 0.6 per million, respectively.

Table 6.—Aplastic Anemia: Annual Incidence Rates According to Region, July 1980 to June 1984

Region	Population, Millions	Interval, mo	No.	Rate/ Million/y*
Ulm, West Germany	5.3	48	56	2.9
West Berlin	1.8	48	18	2.2
Barcelona, Spain	4.1	48	36	2.2
Israel	3.9	48	21	1.6
Budapest, Hungary	2.0	31†	3	0.6
Stockholm/Uppsala, Sweden	1.8	18‡	2	. . .§
Milan, Italy	2.3	45‖	27	3.1
Sofia, Bulgaria	1.1	23¶	5	2.6
Total	20.5	. . .	. . .	2.2#

*Standardized to the age and sex distribution of the study population.
†December 1981 to June 1984.
‡January 1983 to June 1984.
§The incidence was not calculated for Stockholm/Uppsala, Sweden, for methodological reasons (see text).
‖October 1980 to June 1984.
¶August 1982 to June 1984.
#Calculated as a population-weighted average of the age- and sex-standardized region-specific rates.

Aplastic Anemia

Table 6 gives the estimated incidence rates by region. Stockholm/Uppsala is omitted because bone marrow biopsies are not done routinely in Sweden, and many potential cases were not confirmed due to insufficient information. The overall annual incidence of aplastic anemia was 2.2 per million (range, 0.6 to 3.1). Of the 168 cases, 159 were followed up for two years: 78 had died, giving a two-year fatality rate of 49%.

In Table 7 the distribution of analgesic use in days 29 through 180 is given for 113 cases and 1724 controls according to use at any time in that interval, use for at least four days in any seven-day period, and use for four or more days a week for at least four weeks. Histories of any exposure to indomethacin (multivariate rate ratio estimate, 12.7), diclofenac sodium (8.8), and butazones (8.7) were significantly associated with aplastic anemia. In addition, with limited numbers, the rate ratio point estimates for the use of indomethacin (52.0) and butazones (34.5) were higher when the drugs had been taken on four or more days in one week and when such use had lasted at least four weeks (49.9 and 43.4). For the use of dipyrone, other pyrazolones, and acetaminophen, there were no statistically significant positive associations. For the use of salicylates on four or more days in any week, and for the use of any drugs in the category of other nonnarcotic analgesics, the estimates were 2.9 and 2.2, respectively, but these results were not statistically significant.

Excess risk estimates were calculated for those drugs significantly associated with aplastic anemia (indomethacin, diclofenac, and butazones) when used any time in days 29 through 180

before admission. For indomethacin the etiologic fraction of 6% translated into an estimated excess risk for any use in a five-month period of 10.1 per million. For diclofenac, the corresponding estimates were 5% and 6.8 per million, and for butazones they were 7% and 6.6 per million.

COMMENT

Agranulocytosis

The use of dipyrone was associated with agranulocytosis in some of the regions under study, but not in others. Overall, indomethacin and butazones were also associated with an increased risk. In addition, there was an association of borderline significance for salicylate use, which was somewhat more pronounced for use that lasted 14 or more days. There was no statistically significant evidence of association for pyrazolones other than dipyrone, acetaminophen, or the heterogeneous category of newer nonnarcotic analgesics, although for none of these drugs could increases in risk of twofold to fourfold be ruled out.

The associations for dipyrone and butazones were expected on the basis of previous evidence.[1-4,14-22] With regard to indomethacin, however, although there are case reports,[23] there are no studies that suggest an appreciable increase in the risk of agranulocytosis. With regard to salicylates, there are only a few case reports suggesting that they cause agranulocytosis,[1,16,24] and since the statistical significance of the association in this study is borderline, it must be interpreted with caution.

The lack of association with the use

Table 7.—Aplastic Anemia: Analgesic Use in Days 29 to 180 Before Admission

Drug	Cases (N=113)	Controls (N=1724)	Stratified Rate Ratio Estimate* (95% Confidence Interval)	Multivariate Rate Ratio Estimate* (95% Confidence Interval)
Dipyrone				
Any	19	418	0.7 (0.4-1.2)	0.5 (0.2-0.9)
≥4 d in any wk	6	34	2.4 (1.0-5.8)	1.6 (0.4-5.7)
≥4 d/wk for ≥4 wk	1	16	1.1 (0.1-8.8)	0.9 (0.1-12.9)
Other pyrazolones†				
Any	27	355	1.0 (0.7-1.7)	1.0 (0.5-1.7)
≥4 d in any wk	6	26	4.9 (1.9-12.3)	0.7 (0.2-2.7)
≥4 d/wk for ≥4 wk	2	11	4.5 (0.9-21.5)	1.2 (0.1-10.5)
Salicylates				
Any	59	823	1.1 (0.8-1.7)	1.0 (0.6-1.6)
≥4 d in any wk	11	58	3.8 (1.8-8.2)	2.9 (1.0-8.6)
≥4 d/wk for ≥4 wk	5	33	3.9 (1.3-12.1)	2.9 (0.7-10.9)
Acetaminophen				
Any	25	381	1.3 (0.8-2.1)	1.5 (0.8-2.7)
≥4 d in any wk	5	49	2.2 (0.8-6.2)	0.9 (0.2-3.5)
≥4 d/wk for ≥4 wk	2	26	2.5 (0.5-13.4)	3.9 (0.7-21.5)
Butazones				
Any	9	40	4.3 (2.1-8.8)	8.7 (3.4-22.3)
≥4 d in any wk	7	13	12.2 (5.3-28.0)	34.5 (9.4-127)
≥4 d/wk for ≥4 wk	5	4	34.4 (12.5-94.9)	43.4 (7.9-239)
Indomethacin				
Any	7	18	7.2 (3.0-17.3)	12.7 (4.2-38.3)
≥4 d in any wk	4	4	13.6 (4.3-43.4)	52.0 (10.6-255)
≥4 d/wk for ≥4 wk	4	3	16.2 (5.2-50.6)	49.9 (9.0-278)
Diclofenac sodium				
Any	7	17	7.4 (3.1-17.6)	8.8 (2.8-27.3)
≥4 d in any wk	2	4	10.5 (2.5-44.2)	7.2 (0.6-82.7)
≥4 d/wk for ≥4 wk	0	1	0.0 . . .	0.0 . . .
Other nonnarcotic analgesics‡				
Any	9	45	3.4 (1.6-7.3)	2.1 (0.8-5.9)
≥4 d in any wk	6	18	9.8 (3.5-27.1)	2.2 (0.4-11.4)
≥4 d/wk for ≥4 wk	3	14	7.4 (1.8-31.5)	0.8 (0.1-6.1)

*Relative to no use in days 29 to 180.

†Includes aminopyrine/propyphenazone (12 cases, 124 controls); aminopyrine (six, 104); propyphenazone (six, 48); antipyrine (three, 42); aminopyrine plus antipyrine (zero, 16); propyphenazone plus antipyrine (zero, 15); aminopyrine/propyphenazone plus antipyrine (zero, three); aminopyrine/propyphenazone plus propyphenazone (zero, two); aminopyrine plus metiphenazone (zero, one). "Aminopyrine/propyphenazone" refers to compounds the components of which were changed from aminopyrine to propyphenazone during the course of this study.

‡Includes piroxicam (three cases, eight controls); benzydamine hydrochloride (one, ten); naproxen (one, seven); niflumic acid (one, one); indoprofen (one, zero); naproxen plus ketoprofen plus piroxicam (one, zero); naproxen plus oxametacin (one, zero); ibuprofen (zero, six); glafenine (zero, two); clonixin (zero, two); ketoprofen (zero, two); chlorthenoxazine (zero, two); etofenamate (zero, one); sulindac (zero, one); flurbiprofen (zero, one); flufenamic acid (zero, one); ibuprofen plus ketoprofen plus sulindac (zero, one).

of pyrazolones other than dipyrone was surprising. Aminopyrine, in particular, is not only chemically closely related to dipyrone, but has been shown on rechallenge to cause agranulocytosis,[25] and antibodies cross-react with both drugs.[26] However, numbers were too small to assess the effect of aminopyrine separately.

Most difficult to interpret is the wide regional variability in the association with dipyrone use, which is unlikely to be due to chance. It is worth noting that in Ulm, Berlin, and Barcelona, where the rate ratio estimate was 23.7, dipyrone was not commonly used, while in Israel and Budapest, with a rate ratio of 0.8, use was common. This pattern may provide a clue to the explanation for the regional variability.

The possibility that the present results are biased or confounded must be considered. Clinically mild cases may in some instances have been diagnosed preferentially if a suspect drug was taken, but the number of such cases would have had to be substantial to affect the results materially. At the other extreme, it is possible that some very severe cases died before a diagnosis could be made. If the severity of the disease was related to the use of any specific drug, this could have resulted in underestimation of the rate ratio. We judge it likely that virtually all clinically severe cases were ascertained.

Almost 100% of the potential controls were successfully interviewed. Final controls were only included in the analysis if they had conditions judged to be unrelated to prior analgesic use; it was reassuring that the distributions of use were generally similar across the major diagnostic categories.

The symptoms of agranulocytosis (fever, chills, sore throat, and headache) are also indications for the use of analgesics. Despite attempts to date the onset of the illness, it is possible that incorrectly reported or unreported symptoms could have induced analgesic use that was erroneously classified as occurring within the etiologic period, resulting in overestimation of rate ratios. If similar misclassification occurred in controls with conditions such as appendicitis, this would have resulted in underestimation. For these reasons, particular attention was paid to the use of analgesics for three or more days, since there was greater assurance that such use antedated the onset of the illness. The results confirmed the overall findings. It is also reassuring to note that had the controls been restricted to those for whom the index day was known beyond doubt (trauma), the findings would not have been changed materially.

There may have been information bias, since it is widely known that agranulocytosis can be caused by drugs. Before the interviews for this study were conducted, many of the cases had been questioned repeatedly about drug use. Thus, the memories of the cases were stimulated before they were interviewed while those of the controls were not. Three approaches were used to reduce information bias. First, the patients were interviewed within 28 days of admission. Second, a standard and detailed questionnaire was used. Third, three or more consecutive days of drug use, presumably less subject to differential recall, was analyzed. Despite these precautions, information bias probably was not completely avoided. Such bias is of concern mainly for drugs already under suspicion as causes, such as dipyrone, and would have resulted in overestimation of the risk.

Information bias may partially explain the regional variability of the association with dipyrone use if the intensity of questioning of the cases before interview differed according to study center. Another possibility is that the recall of dipyrone use by the controls varied among the regions. The drug was available under many more brand names in Ulm, Berlin, and Barcelona[27,28] than in Israel[29] and Budapest.[30] Controls in Ulm, Berlin, and Barcelona could have used dipyrone-containing preparations with unfamiliar names and not have recalled their use, with resultant overestimation of the risk in those regions.

The possibility of underascertainment of analgesic use among the controls should be checked, if feasible, by comparing the rates with data such as defined daily doses.[31]

Potential confounding by age, sex, region, concomitant drug use, and various other factors was controlled simultaneously by multivariate analysis. It remains possible that confounding was incompletely controlled.

On balance, we judge that the results are not materially biased. In particular, the regional variability in the association with dipyrone use is so great that it is more plausible to assume that some unidentified factor, present in some regions, but not in others, acts together with dipyrone to increase the risk.

The excess risk for dipyrone use, as estimated in this study, is discordant with the findings of others. Discombe[12] and Huguley[13] estimated, respectively, that 0.86% and 0.79% of patients who use aminopyrine for 14 or more days develop agranulocytosis. Huguley suggested that this risk also applied to dipyrone. As has already been pointed out,[32] these estimates were biased. Corresponding estimates for dipyrone derived from the present data suggest that in Ulm, Berlin, and Barcelona, where the association was strongest, the excess risk attendant to at least 14 consecutive days of use is 3.3 per million, or 0.0003% (derived by multiplying the excess risk by three, because, as defined in this study, a 14-day period of use could have commenced up to three weeks previously; the assumption is made that the risk per unit time is independent of the duration of use). In the other regions, the excess risk appears to be even lower.

Böttiger and Westerholm[33] suggested that agranulocytosis occurs in about one of every 3000 dipyrone users. This estimate is also much higher than the present one, but its validity is in doubt. First, there were repeated government warnings about the dangers of dipyrone, and it is possible that dipyrone-associated agranulocytosis was preferentially reported to the Swedish Adverse Reaction Registry. Second, and more important, the consumption of dipyrone declined dramatically during the period of observation, and it remained low thereafter, probably because of the warnings. The denominator of dipyrone users was estimated from prescription records at a time when consumption was virtually at its lowest, whereas the numerator was not, resulting in a risk estimate that was too high.

Other studies have ruled out risks for dipyrone users of more than one in 1000[33] and one in 133 000[34] although they did not provide estimates of the actual risk.

With regard to indomethacin and butazone use, the excess risk of agranulocytosis has not previously been estimated. The data were too sparse to explore possible regional variability for these drugs.

Aplastic Anemia

The analgesics significantly associated with aplastic anemia when taken 29 to 180 days previously were indomethacin, diclofenac, and butazones, with estimated increases in risk of the order of tenfold. In addition, for two of the drugs (indomethacin and butazones), with limited numbers, there was a suggestion that the risk was higher if they were taken regularly and

for a sustained period.

There was no evidence of an association with the use of dipyrone or other pyrazolones. Within the latter category, however, numbers were too small to evaluate individual drugs. For salicylate use of four or more days' duration, the rate ratio estimate was somewhat elevated, but this result could have been due to chance. Similarly, the association with the use of a mixed group of the newer nonnarcotic analgesics other than diclofenac could also have been due to chance. However, since individual drugs in this category have been implicated in case reports as possible causes of aplastic anemia,[23] these agents require further study.

The butazones are a well-recognized cause of aplastic anemia,[20,35,36] and the association identified in this study was strong, although based on small numbers. There have been case reports linking indomethacin use with aplastic anemia,[23,37,38] but the strength of the association observed here is surprising. Diclofenac has been implicated in case reports,[39] and the present study gives a quantitative estimate of the risk. This result needs to be confirmed in further studies.

Potential methodological problems must be considered. The diagnosis of aplastic anemia is virtually inevitable in all cases and selective enrollment dependent on drug use was therefore unlikely. The incidence reported here was lower than in other studies,[35,40,41] but this could have been due to the use of different diagnostic criteria. As for the controls, their conditions, most of recent onset, should have been independent of the use of analgesics 29 to 180 days earlier. Consonant with this, the distributions of analgesic use across diagnostic categories were similar.

About 8% of the cases were not interviewed because of death and 22% because they could not be interviewed within 28 days. If the use of any drug was selectively associated with severe or rapidly fatal aplastic anemia, this could have resulted in underestimation of the risk.

It was impossible to time the onset of aplastic anemia because symptoms such as fatigue or easy bruising are too vague. In the days or weeks before admission, episodes of infection or fever due to as yet undiagnosed aplastic anemia could have provoked the use of analgesic or antipyretic drugs. For this reason, drug use that took place within the 29 days before admission was not analyzed. It must be acknowledged, however, that 29 days is an arbitrary cutting point and that in some individuals the illness may have remained undiagnosed for many months. Thus, drug use that commenced more than a month before admission may sometimes have been provoked by early symptoms and the effects of some analgesics (eg, salicylates) could have been overestimated. All of the results for aplastic anemia must therefore be interpreted with caution. However, for the use of indomethacin, butazones, and diclofenac, the rate ratio estimates were so high that it is doubtful that they could be entirely accounted for by occult aplastic anemia having provoked their use.

It is widely suspected that some analgesics can cause aplastic anemia. Butazones, for example, were given considerable publicity while the study was in progress. Had there been differential recall, it should have been least marked among those who used analgesics the most. The associations with the regular use of indomethacin and butazones for more than a month suggest that information bias was not a major problem.

As with agranulocytosis, confounding by concomitant drug use and various other factors was controlled by multivariate analysis. Again, it is possible that confounding was incompletely controlled.

This study is the first to provide excess risk estimates of aplastic anemia in users of analgesic drugs. Their interpretability is limited, however, because of small numbers. In addition, the present findings suggest that the magnitude of the risk may be a function of both the frequency and the duration of use, at least for certain drugs. How to select an appropriate measure of risk is therefore unclear. Given the uncertainties as to onset of the disease and timing of relevant exposure, we elected to estimate the excess risks associated with use of a given drug on one or more days in a five-month period.

GENERAL CONCLUSIONS

In the regions in which this study was conducted the incidence rates of agranulocytosis and aplastic anemia are low. Aplastic anemia is less common than agranulocytosis, but the fatality rate is higher. The fatality rates of the two diseases, as well as their incidence, must be considered in interpreting the results for analgesic use. However, inferences about the public health impact of analgesic use cannot be more widely generalized to other regions of the world if a fatal outcome of agranulocytosis is more common because of factors such as malnutrition or inadequate medical care.

In considering public health implications, it is necessary to compare analgesics not only in terms of blood dyscrasias, but also in terms of other serious adverse effects. What matters ultimately is the total risk of morbidity and mortality. Many of the conditions that have been attributed to the use of analgesics may occur more commonly than agranulocytosis or aplastic anemia. These include thrombocytopenic purpura, hemolysis, shock, nephrotoxicity, hepatotoxicity, and gastrointestinal disorders such as major upper gastrointestinal tract bleeding. The latter condition is the most important since of those that are life threatening it is by far the most common.[42] Quantitative estimates of the risk of bleeding have been published for some of the drugs considered here (eg, aspirin[43,44]) whereas for others (eg, dipyrone) none are available.

There were some large relative increases in risk in this study: agranulocytosis among users of dipyrone (in some regions), butazones, and indomethacin, and aplastic anemia among users of butazones, indomethacin, and diclofenac. However, it is more important to note that the absolute risk associated with all of these drugs appear to be very low: for exposures occurring in a seven-day interval, the estimated excess risk of agranulocytosis ranges from 0.2 to 1.1 per million; for exposures occurring in a five-month interval, the estimated excess risk of aplastic anemia ranges from 6.6 to 10.1 per million. It is the latter estimates that provide measures of the incidence of blood dyscrasias attributable to these drugs.

This study was sponsored by Hoechst A... Frankfurt, Federal Republic of Germany. Part... support was also provided by the governments ... Hungary and Bulgaria and by the Corporation ... Swedish Pharmacies. The study was supervised ... an Honorary International Advisory Board whose members are Sir Richard Doll, FRCP, FRS, Oxford, England, Chairman; Per Knut M. Lund... MD, Oslo; and Sven Moeschlin, MD, Solothu... Switzerland.

This study would not have been possible with... the cooperation of over 300 hospitals in ... participating centers.

Participants in the International Agranulocytosis and Aplastic Anemia Study are as follows:

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Editorial

Analgesic Risks and Pharmacoepidemiology

Knowledge of uncommon adverse drug reactions ordinarily derives from case reports based on clinical observations. Size limitations of clinical trials preclude identification of rare adverse reactions.[1] Yet individual case reports have two problems. First, an observed clinical event may be coincidental to a particular drug exposure, be linked to the disease being treated, or be due to other drugs. Only in the unusual instance when rechallenge and reappearance of the event are described can causality be clearly inferred from a case report. Second, individual case reports cannot generally provide a basis for incidence estimates.[1] For prospective clinical decisions, the issue is not whether a drug might cause a reaction, but how often this happens.

See also p 1749.

Thus, the extraordinary study of the relationship between analgesics and aplastic anemia and agranulocytosis in this issue of THE JOURNAL is most welcome and important.[2] Because these conditions are rare, a case-control study is the only practical means to examine their epidemiologic characteristics and associations. To assemble 588 carefully defined cases at 300 hospitals involved work in seven countries by more than 40 investigators during a four-year period. Patients and nearly 2000 controls were interviewed to determine drug exposures and other risk and disease factors. Effort was made to avoid bias in case and control selection and data collection. This enormous study sought all cases in a total defined population of 22.3 million so that reasonable estimates of incidence could be derived.

The study found that agranulocytosis and aplastic anemia are indeed rare conditions with overall annual incidence rates of 6.2 and 2.2 per million population. For agranulocytosis, strongly positive associations were found for phenylbutazones, indomethacin, and dipyrone, but their excess risks were small, ranging from 0.2 to 1.1 per million. Considerable variation by region in the risk ratios for dipyrone was found and discussed, but it remains unexplained and disturbing. While the variation may be due to differences in populations or medical practice, one must be concerned about hidden biases or methodological problems that could affect other results of the study. For aplastic anemia, excess risks of 6.6 to 10.1 per million were found for phenylbutazones, diclofenac sodium, and indomethacin, and increasing risk for phenylbutazones and indomethacin was found with increasing intensity and duration of use. While the indomethacin results are somewhat surprising, they are consistent with evidence from an earlier study of aplastic anemia and agranulocytosis done by Inman[4] in the United Kingdom. Phenylbutazone risks appear to be lower than previously found and thus merit critical examination. The relatively low use rates during the period of the study for many newer nonsteroidal antiinflammatory drugs prevented the drawing of meaningful conclusions about the relationship of these drugs to hematologic toxicity.

Why is this study important to the clinician? First, it examines multiple drug exposures: too often only a single drug is studied. If defined risks are to be clinically useful, they must be available across a therapeutic drug class so that comparisons can be made. Next, though aplastic anemia and agranulocytosis are rare effects of analgesics, benefits must always be weighed against quantified risks. Hematologic toxicity is noted in labeling information for hundreds of drugs, yet because precise incidence data are seldom available, clinical decisions about monitoring blood counts and use of drugs are based on intuitive perception of risk.

Lest the study be misinterpreted, it must again be emphasized that what counts is total drug risk. Gastrointestinal and other organs are far more frequently adversely affected by analgesics than the hematologic system. Even the highest rates found in the study do not greatly exceed the mortality rate of five per million exposures for these drugs. While no firm cutoff can be set for declaring any drug absolutely safe, it should be recognized that when drug-induced mortality is found to be below five or ten per million, differential distinctions about the safety of one drug compared with another will be difficult to ascertain and support scientifically. Thus, choices of analgesics, once the need for them is clear, should not be made solely on the basis of the hematologic toxicity described in this study.

The presentation of an impressive pharmacoepidemiologic study reminds us how few such studies are carried out. To examine risks of marketed drugs, appropriate cohorts or case series and comparison populations must be located in the community. Dealing with confounding by indication and other complexities of observational studies of ill patients requires carefully designed approaches and sophisticated analyses. Who will fund and conduct such studies? Usual sources of research support find that most pharmaceutical safety issues are too mundane or are lacking in basic scientific significance. Regulatory bodies have few funds for research. The pharmaceutical industry, while not homogeneous, largely commits its postapproval research funds to clinical trials having potential for product enhancement. The result is that there are few academic or industry-based pharmacoepidemiologists in the United States or elsewhere. There are no easy remedies for these funding and manpower deficiencies. Certainly the starting point is a recognition that epidemiologic studies of postmarketing drug safety are in the interest of the medical community, the government and the pharmaceutical industry. Drug development does not stop when marketing begins. To improve drug therapy, pharmacoepidemiology must be fostered and practiced.

The opinions expressed are those of the author and do not necessarily represent those of the Food and Drug Administration.

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WHY ANALGIN SHOULD BE BANNED

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by
Dr. Anant Phadke
Medico Friend Circle.

A bit of history

Analgin is a pyrazolon derivative. Other generic names of Analgin are: Dipyrone, Metrazol, Methapyrone, Sulpyrine and Formamidopyrine Methanesulfonate Sodium.

A group of compounds called Aminophenazone is close congener of Analgin. Aminophenazone is also known as Dipyrine, Aminopyrine, Amidopyrine, Amidopyrazoline, Amidofebrin. The two groups of drugs have similar pharmacological and toxicological properties, including the potential to cause fatal agranulocytosis. Analgin differs only in being more soluble and available for parenteral administration.

Aminophenazone/Amidopyrine was used for 70 years for its potent antiinflammatory and analgesic action. But early in the thirties, it was found that Amidopyrine causes agranulocytosis; and was identified as a major cause of drug-induced agranulocytosis. It was therefore placed under prescription control by the F.D.A. of the U.S.A. in 1938. /1/. With the advent of better, safer antiinflammatory, analgesic agents, this drug gradually fell into disuse. But in India, it was widely sold by drug companies till fixed dose combination of amidopyrine was banned by the Drug Controller of India from 31st October 1982. In 1979-80, 95 tonnes (!) of amidopyrine was imported in India.

ANALGIN, which is the sodium sulfonate derivative of this notorious Amiodopyrine, was introduced by Hoechst in 1922. Since 1931, the group of pyrozolones to which Analgin belongs, has been suspected of causing agranulocytosis, and in 1934 this connection was proved. Yet till the 1960's this drug was widely used. But evidence accumulated in respect of Analgin-induced agranulocytosis and hence gradually this drug was also discarded in the West in 1960-70's (Sweden, Norway, Australia, New-Zealand, U.S. Canada...etc.). Thus in the 1973 edn. of the AMA Drug Evaluations, American Physicians were told :

" Its only justifiable use is as a last resort to reduce fever where safer measures have failed. Because dipyrone may produce fatal agranulocytosis and other blood dyscrasias, its use as a general analgesic, antirheumatic, or routine antipyretic cannot be condoned. " (p.262-267.) "

In 1977-edition of WHO drug evaluation, it was stated that the drug had become obsolete in the U.S.A. (p.341). In the 1980 edition, it is not even listed. From 1965, onwards it was withdrawn or banned in many countries. But it continues to be sold in India in large quantities and used for trivial reasons. It is also available in drops (Tridrigin) and is included in most of the antispasmodics- (Baralgan, Trigan, Maxigin, Spasmigol...etc.)

Analgin induced agranulocytosis :

Agranulocytosis is the most important adverse reaction of Analgin.

The incidence of aminopyrine : induced agranulocytosis has been variously estimated between 0.01 % and 0.86 %, the mortality rate being 20% - 50%. /3/.

~~is sudden and acute.~~ Exact mechanism of this disease is not known. It is likely that the antibodies resulting from the drug allergy destroy the white cells in the peripheral blood and probably in the bone marrow too. It could also be due to development of lupus syndrome (a systemic illness characterised by skin lesions where antibodies produced, damage the patient's own tissues.) The third theory being toxic depression of bone marrow resulting from prolonged administration of a drug.

The possibilities of occurance of agranulocytosis are greater in adults above age of 40 years and more often in women than in men. /2/ 41

The clinical symptoms of ~~the disease~~ agranulocytosis are- onset of abrupt high fever, rigors, occasional evidence of acute localised infections like : pharyngitis or an abcess. Patient may even die

due to infection. If patient survives the infection, then he/she could be cured within 2-3 weeks of complete withdrawal of the drug. Even after recovery the sensitivity persists for long periods as long as 20 years sometimes i.e. if the patient takes this drug again then disease will promptly recur.

The Director of the Bureau of Drugs in the U.S. found that . . . " agranulocytosis cannot be effectively prevented by frequent examination of treated patients since this condition can occur within a few hours following administration of this drug to a sensitive individual. /5/.

. . . . . .

The so-called Boston Study (International Study of Agranulocytosis and Aplastic Anemia, ~~Findings~~, the ~~IAAAS~~ I.S.A.A.A. Study)

Estimates of the attendant risk of agranulocytosis very considerably and a large multicentric study was planned to provide a more precise estimate. ~~The study is sponsored by the Hoechst.~~ This was a case control study of drug induced agranulocytosis, with particular emphasis on pyrozolones (including dipyrone). ~~It was in its final stages.~~ The study covered a population of 22.4 million people from Israel, West Berlin, Milan, Barcelona, Budapest, Sofia, Stockholm and an area around Ulm. The data ~~was~~ were collected for a period of five years.

It is a little misleading to call this study as Boston study since only the data of this study were analysed at Boston. It was primarily financed by Hoechst, with some finding help from Hungary and Bulgaria and Sweden. We, therefore, call it as Hoechst Study. Hoechst and other manufacturers are misusing the findings of this study to create on impression that this study has proved that Analgin is not more hazardous than other analgestics. But it should be pointed out that though source of the earlier estimates can be faulted and were overestimates, the data, the analysis and conclusions of this ISAAA-study and also highly controversial; and this study is in no way conclusive.

Limitations of the ISAAA-study :

Dr. A.Herxheimer of Charing Cross Hospital Medical School, UK and Dr. John Yudkin have pointed out that the study does not provide the true incidence of drug induced edranulocytosis, because " the study excludes all patients (a) who die of agranulocytosis without receiving medical care, (b) who die of it without having a white cell count and (c) who have undiagnosed agranulocytosis and recover from it...! Thus according to them the study would yield only a 'minimum estimate' of both 'incidence & morality' while the 'actual incidence could be higher.

Dr. Willbert Bannenberg has pointed out many other limitations of this study-6.

(Contd....

* The study does not look into other side-effects of dipyrone such as shock, hypotension, Urticaria, Lyell syndrome, Moscowitz syndrome..etc.

* The data in the intermediate results published in the Lancet (25th Feb'84) and those in the final report are inconsistent. There is a three-fold increase in the use of Analgin in the control group in the final report as compared to the intermediate report !

* Whereas 400 cases of agranulocytosis were required to assess the risk properly, in the final analysis, due to a large percentage of exclusions, only 221 cases are analysed in the final report.

* There is extreme variability in the incidence of agranulocytosis not only amongst different countries but even between community and hospital cases in the same countries.

* The control group is probably not representative of the general population. 27% of them mentioned the use of an analgesic the week before their interview ! A ~~high~~ higher consumption of analgesics in the control leads to a lower figure of relative risk.

* Some data are clearly unreliable. For example: the data collected through interviews indicated that the consumption of pyrazolone in Israel was 5 times more than in other countries, whereas the Index of Medical Specialities (IMS) Sales data shows that Israel actually uses 3 to 4 times less dipyrone ! - the difference in these two data is twenty-fold !!

It may be mentioned that one of the two chief-investigators and its study-Director, Prof. M.Levy was biased in favour of Analgin. This is clearly seen in his paper : "Adverse Drug Reactions to Analgesic - Antipyretic Drugs." This paper, circulated by Hoechst, starts by claiming (on page No.1) that " Dipyrone is widely used in many countries, including numerous countries where medical knowledge and practice are well advanced." But it does not mention that it is banned or withdrawn or severely restricted in developed countries

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like : Australia, USA, UK, Greece, Denmark, Norway, Sweden, West Germany, Japan. In this paper, Prof. Levy likewise, selectively gives facts and figures which favour the continued use of Analgin.

Misleading propaganda :

Thus this so called Boston-Study is by no means conclusive. Secondly, even the results of this controversial study are being propagated by Hoechst in a misleading manner. Hoechst claims that this study has shown that the risk of agranulocytosis due to Analgin is only 1 in 1 million. It must be noted that this risk of 1 in 1 million exists if one or more tablets are taken in one week only. If dipyrone is used for longer periods, the risks will be greater. This was confirmed by Shapiro, the epidemiologist and Administrative Director of this study, during the press-conference in Stockholm. Wilbert Bannenberg[7] has estimated the risk as of 1 case of agranulocytosis per 70000 packages of dipyrone--an estimate based on the data of this Hoechst-Study, but one which takes into account the usual pattern of consumption of analgin and hence is a more appropriate way of quoting risk figures. Lancet has also pointed out that " The estimate of the excess risk from dipyrone is expressed rather oddly, as 1.4 per million takers during a seven day interval. The calculation underlying this estimate is not explained. The peculiar denominator is difficult to apply to real life. The risk of exposure during one year could be upto 50 times higher. It would be expressed more clearly as the number of cases per million defined daily doses (DDD) or per 100,000 packs sold."[8] On 19th Oct'86, the German Federal Health Office (BGA) conducted its second hearing on the risks and benefits of dipyrone. In this hearing also the presenting of risks in the odd way of so many million takers per week was criticized by many scientists. After expressing the risk in usual terms, the risk was estimated to be in 30,000 to 1 in 70,000 per user and year. The speaker of the FRG's Pharmacists Association concluded that it took him a long time to understand that

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the risk of agranulocytosis is as high as it was already estimated in the 1981 hearing. -9

Even if we accept the controversial, minimum risk of agranulocytosis as given by this Hoechst-study, we get 7000 cases of analgin-induced agranulocytosis per year because every year, according to Hoechst, about 10000 tonnes of Analgin is consumed in the world, more than 25 tonnes a day ! The mortality in agranulocytosis in Europe, Eastern-block countries and third-world is around 10%, 25% and 50% respectively. This means 1500 to 2000 deaths per year due to Analgin induced agranulocytosis!!

Agranulocytosis in India:

Many medical practitioners say that they have used plenty of analgin for years, but have not come across a single case of agranulocytosis. This is because of the fact that by and large, cases of agranulocytosis go undetected in India. The clinical picture of agranulocytosis abrupt onset of high fever, throat-pain, rigors, occasional evidence of acute localized infection- is difficult to distinguish from that of infective fever, so commonly found in India. The patient may recover spontaneously or die of fulminating infection, without being investigated haematologically. Since the onset of agranulocytosis is not immediate, it is hardly ever suspected.

Analgin induced agranulocytosis does occur in India. One has to only look for it systematically. This is what is being done, by Prof. B.C. Mehta, the leading haematologist from Bombay. He has communicated his experience " In my haematological-practice, I encounter 12-15 cases of agranulocytosis in a year. Of these, 10-12 cases are caused by Dipyrone or Dipyrone containing drugs."/10/ Dr. Mehta has estimated that even assuming the risk estimation of the Hoechst-study to be correct, in India, one person develops Analgin-- induced agranulocytosis per day.

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Risk due to Aspirin, Paracetamol and Analgin:

Hoechst has tried to create an impression that all Non-steroidal anti-inflammatory Drugs (NSAID) cause agranulocytosis, and therefore is nothing special about dipyrone."[11] Even Prof.M. Levy has also tried to argue in this fashions (in his paper mentioned earlier). He has even quoted, uncritically, one estimate which says that paracetamal induced agranulocytosis may account for as much as 10% of all cases of this disorder. But the fact is that none of the standard sources seriously implicate Aspirin, paracetamol in the causation of agranulocytosis. Even in this Hoechst-Study, the relative risk (relative to not taking the drug) of different analgesics for causing agranulocytosis shows a vast difference between Analgin and other minor analgesics. The following table gives the relative risk as found in this study :-

Relative Risk of Agranulocytosis[12]

Name of the Drug	After any exposure to the drug	for three or more day's use.
Dipyrone (in Ulm, Berlin, Barcelona Centres). ...	23.7	20.4
Dipyrone (in Israel, Budapest Centres) :	0.8	1.2
Salicylates ...	1.6	1.9
Paracetamol ...	1.0	0.8
Butazones ...	3.8	6.3
Indomathacin ...	8.9	14.2
Other NSAIS	0.9	0.6

-12

It has been argued by Prof. Levy (Adverse drug reactions...op.cit.p.3 to 5) that Aspirin, also causes death on a/c of its nephrotoxicity and by causing acute gastrointestinal bleeding. But he conveniently

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forgets that to a varying extent, all NSAIDs cause nephropathy and gastric bleeding. (Gastric bleeding is partly due to the systemic effect of the anti-prostaglandin effect of NSAIDs and even injectable Analgin can also cause gastric bleeding.) Secondly, the risk due aspirin induced gastric bleeding or the risk, due to Reye's Syndrome can be considerably reduced by avoiding its use in susceptible patients, whereas analgin induced agranulocytosis is unpredictable and unpreventable. Similarly accidental or suicidal poisoning due to paracetamol overdosage cannot be compared to the risk associated with Analgin.

Other side-effects of Analgin :-

Injectable dipyrone can cause severe hypotension, as well as anaphylactic shock and for this reason, injectable preparations for dosages higher than 1 gm., and intravenous preparations have been withdrawn from Italy, Saudi-Arabia and Egypt.[13] In many developed countries, analgin in any form is not marketed at all (see later.) It may be noted that the German Federal Health Office recorded 94 lethal cases after intake of dipyrone in FRG from July'81 to July'86; Out of these 46 deaths were due to haemotological reactions whereas 39 deaths were due to allergic reactions.[14]

Dipyrone can also aggravate a bleeding tendency or prothrombin deficiency. It is contraindicated for use with chlorpromazine as it can cause severe hypothermia.[15]

There are some other problems with Analgin as enlisted by Hannenberg.[16]

Genuine therapeutic need ?

Analgin is a very potent antiinflammatory analgesic, antipyratic. But now safer, powerful agents are available with the advent of propionic acid derivatives (Ibuprofen, Ketoprofen...etc.)

...

" even after 100 years of use, the mode of action is still unknown.

-unknown is also which metabolite causes agranulocytosis or other side-effects (and how.) It is known, for example, that the drug aminophenazone, banned worldwide because of severe side-effects, has some similar metabolites as dipyrone: does this mean that dipyrone metabolites cause the same side-effects ?

-basic pharmacology data (e.g. use in renal, liver, or elderly patients) carcinogenicity, teratogenicity are not yet known, as it was developed before the 'thalidomide scandal' and could therefore get easier registration.

-there are 2 Japanese reports that link dipyrone to a significant increase in hepatoma toxicity studies with mice. Hoechst has never challenged these reports.

-interactions with other drugs such as anti-diabetics have never been investigated....."

Genuine therapeutic need ?

Analgin is a very potent antiinflammatory analgesic, antipyratic. But now safer, powerful agents are available with the advent of propionic acid derivatives (Ibuprofen, Ketoprofen...etc.), for oral use.

(.....ctd.

When parenteral analgesic is required for acute, severe pain, Inj. pentazocine,(Fortwin) a very potent, safer analgesic is now available. Many surgeons in India now use Pentazocine (along with stemetil/siquil to prevent pentazocine induced vomiting) postoperatively. (Most doctors do not apply for registration to get morphine, pethidine.) Buprenorphine ~~the~~ an extremely potent alternative to morphine is now widely available in India. (17ps. per tablet, Rs. 4-40 per ~~the~~ ampoule).

It has been argued that Inj. Baralgan, ~~is essentialxtoxtreatxrenalxcolic~~ which contains Analgin plus a spasmolytic agent, is essential to treat renal colic. But the combination of Inj. Pentazocine with Injection Buscopan is used by many doctors with equally good results. It may be noted that in many countries Analgin, Baralgan are not marketed, yet the doctors there successfully treat such cases. Same is the case with post-operative and other such cases of acute, severe pain. Thus there is no merit in the argument that analgin is essential to treat such cases.

Hoechst has been claiming that Analgin has an antispasmodic action and hence Analgin-containing Baralgan is more effective. This claim has not been scientifically substantiated. When Association for Consumer Action for Safety and Health (ACASH) Bombay asked Hoechst to provide reference-papers to scientifically back up this claim, Hoechst did so only after a lot of prodding by ACASH. These reference-papers were given by ACASH to leading Pharmacologists in Bombay and Baroda. All these experts criticized these papers. For example Satoskar, the author of the Textbook of Pharmacology stated that only : "...one reference indicates that dipyrone has smooth muscle activity. This reference is of 1956...The references do not give any comparison between various NSAIDS as regards this property....." Dr. Shaligram, professor of Pharmacology, Grant Medical College, Bombay commented : "....(this reference) is published in current Therapeutic Research--a journal known to publish anything from rubbish to sublime...." About a second set of references provided by Hoechst, Prof. Shaligram had this to say---"...This is the most unscientific of reviews. The author's claim regarding spasmolytic effect (of dipyrone) is empirical and

lacks details required for verifying the authenticity."

It is no wonder, therefore, that none of the standard textbooks of Pharmacology mention about any spasmolytic action of dipyrone.

Some doctors feel that injectable Analgin is necessary to reduce high fever. This is not true. Oral aspirin, paracetamol and cold sponging is quite effective. In case of hyperpyrexia, ice-cold sponging, ice-cold enema, rehydration is more important than drugs; hyperpyrexia can not be countered with anti-prostaglandin effect of these drugs.

Conclusion :

We have to conclude that since the risks associated with use of analgin are of very serious nature and since there are now better substitutes available, Analgin should no more be used. That is why standard authorities have, over a period of time, cast their opinion against the continued use of Analgin. According to the 5th edition of Goodman-Gillman, antipyrine, dipyrone can be used in certain cases. In some cases of prolonged intractable fever, as in Hoogkin's disease and Periarteritis nodosa, they are capable of controlling the disability and may be justified."[17] Even in such cases they should be employed only after safer drugs and other measures have proven ineffective. They should be used under proper supervision and monitoring. However, the F.D.A. of U.S. regards that " true risk associated with this drug far outweigh any benefit derived from its use, including use in Hodgkin's disease and similar malignant diseases."[18] The 7th edition (1985) of Goodman-Gillman does not mention this use of Analgin.

Action taken in other countries : [19] Analgin has been prohibited, withdrawn or not available in Australia, U.S.A. U.K., Denmark, Norway, Sweden, Venezuela, Singapur and is under restricted use, strictly under prescription, in Israel, West Germany, Saudi Arabia, Japan, Phillippines, Peru, Greece, Mexico.

...

Following reports of anaphylactic shock, Italy, Egypt, Saudi Arabia, have prohibited manufacture of injectable preparations with dosages higher than 1 m and intravenous preparations.

So dear ~~prescriber~~ doctor, would you keep ~~r~~ risking your patients' life for such low medical benefit of using Analgin ? Certainly not; Please STOP USING ANALGIN in any form. Ask the Government to ban this obsolete drug.

STOP USING ANY OF THESE DRUGS :

Avafortan,	Baralgan,
Bral,	Anadex,
Codolsic,	Analgin,
Novalgin,	Novalgin-quinine,
Panagine,	Promalgin,
Sedyn-A-Forte,	Ultragin,
Zinalgin-A,	Esgipyrin,
Kilpane,	Oxalgin,
Spasmicol,	Spasmolysin,
Spalcin,	Buscopan-compositum,
Orphalgin,	Symalgesic,
Algesin-O ....etc.	....etc...

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2) Goodman-Gillman, The Pharmacological Basis of Therapeutics, 5th Edn. 1975, p.347, 348.

2) " Consolidated List of Products whose consumption and/or sale have been banned, withdrawn, severely restricted or not approved by Govt." United Nations, IInd issue,'86, 62.

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4) Dr. Sunil J.Parekh, Agranulocytosis - Diagnosis, Management and Pathogenesis.

5) U.N. Consolidated list, op. cit. p-62.

6) Wilbert Bannenberg, Dipyrone, Hoechst & the Boston Study, mimeo, Health Action International, Oct'86, reprinted in the Medico Friend Circle Bulletin, Decr.'86.

(Ctd.....

7) W. Bannenberg, op. cit.

8) Lancet, Octo. 18, 1986, p.899-900

9) PHARMA BRIEF, Health Action International (D), No 6, Sept./Octo. 1986, p. 3.

10) Letter from Dr. B.C. Mehta to the Editor, Journal of Association of Physicians of India (J.A.P.I.) : 19.5.84, ~~No 6, Sep/Octo 86 p 3.~~

11) How safe is a safe drug ? Hoechst A.G., Frankfurt, p.6

12) SCRIP, No.1128, August 13, 1986, p.23. (report of the ISAAA-study)

13) UN Consolidated List, op.cit. pp-62, 63

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16) W.Bannenberg, op.cit.

17) Goodman-Gillman, op.cit.

18) UN Consolidated list, op.cit. p-62

19) UN Consolidated list, op.cit. p-62, Fortyfour problem drugs, International Organization of Consumers' s Union (IOCU), Penang, Malaysia, 1981, p.36.

The patient who had been taking Analgin previously with no adverse effects. Agranulocytosis develops suddenly after only one dose and there is a fall in the leucocyte count and disappearance of granulocytes from the blood within 6 to 24 hrs. The subsequent clinical manifestations depend upon whether or not infection develops. Ordinarily, granulocytes appear in the blood in 5-10 days after the drug is discontinued and if death does not occur from infection, recovery is rapid. Infection manifests as a sore throat of sudden onset, high fever, prostration and necrosis without pus. The mortality rate is 20-50%. (3).

HISTORY: Aminopyrine was introd. as an analgesic & antipyretic in 1897, it became very popular in 1920s and was ~~widely~~ used world wide by 1930.

Agranulocytosis was 1st described by W. Schultz in 1922. Madison & Squier in 1933 established a causal relation betw. aminopyrine & agranulocytosis.

1935 - Kracke & Parker estd. its relationship beyond all doubt. After this report, the use of Aminopyrine virtually stopped & so did agranulocytosis, till other drugs like sulphonamides & antithyroids drugs capable of producing this syndrome led to detection of some cases of agranulocytosis.

Since 1938 - OTC sale in USA prohibited.

1922 - Dipyrone or Analgin was introduced by HOECHST. Not being recognised as a derivative of Aminopyrine, it gained popularity.

The American Med. Assoc Registry on Adverse Reactions recd. only 10 reports of leucopenia ~~in~~ some in children from 1955-59. Since 1960-64, 18 cases were reported, 7 in children, with the increase in the import of dipyrone from nil in 1958 to 18,879 lbs in 1962.

1964 - Amer. council of drugs - section on adverse reactions studied the case of Dipyrone (Analgin) and questioned the justify. of continued use of this drug, esp. since articles urging use of dipyrone are chiefly taking advantage of its antipyretic action.

1) Goodman & Gilman
2) JAMA 8 21 Sept 84 - Hingsley
3) Review Med. Pharm 6th Ed 1978 - Meyers / Barwetz / Goldfien
4) Dipyrone, Hoechst & Boston Study - Wilbert Bannenberg ; HAI, The Hague Netherlands.

ANALGIN – THE DRUG

Analgin or Dipyrone belongs to a class of chemicals (used as drugs) called Pyrazolones. (1) Of these, Aminopyrine was introduced as an analgesic antipyretic agent in 1897.* It's sodium Sulfonate derivative with similar pharmacological & tox. props. and proportional to cause toxic sym. properties is Dipyrone or Analgin. (2) Analgin is more soluble than Aminopyrine, rendering it amenable to use as injections and liquid preparations like Syrups.

In both animals & man, the pyrazolon derivatives exhibit analgesic, antipyretic and anti-inflammatory properties similar to those of the salicylates, though they have not been subjected to adequate clinical trials by current standards (they were introduced in the pre-Thalidomide era).

The therapeutic effects are similar to those of aspirin, i.e. these drugs are analgesic, antipyretic and antiinflammatory (2). The pyrazolon derivs are not organic acids, are only slightly bound to plasma proteins, do not cause gastric irritation or produce acid-base or metabolic effects of salicylates and do not have uricosuric prop^{s} (2)

Among the pyrazolons, adequate documentation is available on ANTIPYRINE, which is used as a pharmacol tool for measurement of total body water since it is distributed in various tissues in proportion to their water content. It is rapidly absorbed from the G.I. tract, attains peak plasma levels in 1-2 hrs, is less than 10% bound to plasma proteins. 30-40% of the drug is conjugated in the liver and eliminated in the urine, while 5% is eliminated unaltered. The fate of a significant fraction of the drug is not known. The plasma half life for the unchanged drug is 7 to 20 hrs. Antipyrine causes induction of the hepatic microsomal enzyme systems and modifies the bio-transformation of other drugs, including the oral anti-coagulants. (1)

Clinical uses: The pyrazolon drugs exert an antipyretic effect in some situations in which aspirin is not completely effective – eg. Hodgkins dis. with fever unresponsive to salicylates or chemotherapy. *persistent & recurrent

If used at all in the Rx of intractable fever, aminopyrine or ~~dyp~~ dipyrone should be employed only after safer drugs and other measures have proven ineffective and only with proper supervision & monitoring. Administration of Dipyrone & chlorpromazine can result in serious hypothermia, and such use is contra-indicated. Dipyrone can aggravate a bleeding tendency or prothrombin deficiency.
Other effects in a soviet ~~study~~ of 4 oral given dipyrone showed skin rashes 38%, Dyspepsia 12% fever 9%, anaphylactic shock 7% & bronchospasm 4%. (4)

The most important adverse effects is AGRANULOCYTOSIS. – This is an allergic reaction characterised by the presence in plasma of anti-bodies to granulocytes. The incidence of agranulocytosis has been variously estimated between 0.01% to 0.86%. The mortality rate is 20 to 50%. (1)

* The other drugs belonging to this gp are: Antipyrene, Phenylbutazone, oxyphenbutazone & Sulfinpyrazone. (2)

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ANALGIN--A STUDY FOR DAF-K

1. The Drug

A class of chemicals called PYRAZOLONES have been used as medicines for over ninety years. Pyrazolones include drugs like Antipyrine, Aminopyrine, Phenylbut zone, oxyphenbutazone, sulfinpyrazone and a derivative of aminopyrine called dipyrone or analgin. The pyrazolones share similar pain killing, fever reducing, inflammation reducing and also toxic properties. Analgin being more water soluble is amenable to use in injections and liquid oral preparations (for children). They are rapidly absorbed in the stomach and intestine and spread in various tissues of the body in proportion to their water content. While 30 to 40% of the drug is altered in the liver and eliminated in the urine, 5% is eliminated unaltered. The fate of a significant fraction is not known.

The range of actions of Pyrazolones is similar to that of Salicylates (Aspirins) except in reducing fever in diseases like Hodgkins disease and Periarteritis nodosa, where aspirins are not completely effective.

The most important and potentially fatal adverse effect of Pyrazolones (Analgin) is Agranulocytosis. This is a condition where the Granulocytes which form the major part of the white blood cell population and are the first line of the body's defence against infection are destroyed. It is an allergic reaction and can occur suddenly even after a fraction of a dose in any person who has been previously taking Analgin with no bad effects. Within 6 to 24 hours, the white blood cell count fall and granulocytes disappear from the blood. They start reappearing 5 to 10 days after the drug is discontinued and rapid recovery occurs.

The incidence of agranulocytosis has been variously estimated from 0.01% to 0.86%. If infection occurs now, it starts as a sore throat of sudden onset, high fever and prostration, which even on proper treatment carries a mortality of 20 to 50%.

The other adverse effects of Analgin documented in a study are: skin rashes, dyspepsia, fever, analphylactic shock and bronchospasm. Analgin can aggravate a bleeding tendency and produces a serious fall in body temperature when given along with Chlorpromazine. Liver cancer in mice has also been reported by Japanese.

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Even now--

a. the mode of action is not known;

b. which are the metabolites which cause agranulocytosis and how is not known;

c. basic pharmacological data, like potential for causing cancer, congenital malformations, kidney and liver damage and damage in elderly patients are not known;

d. interactions with other drugs for diabetes, hypertension etc., have not been investigated because pyrazolones were introduced in the pre-Thalidomide era when registration was easy.

2. History and present status

1897 Aminopyrine was first introduced and became very popular in 1920s for pain killing and fever. By 1930s its use was world wide.

1922 Agranulocytosis was first described by W. Schulz

1922 Dipyrone or Analgin was introduced by Hoechst. Not being recognised as a derivative of Aminopyrine, it gained popular use.

1933 Madison and Squier established a causal relation between Amidopyrine and agranulocytosis.

1935 Kracke and Parker established its relationship to agranulocytosis beyond doubt

1938 O.T.C. sale in U.S.A. was prohibited.

1955-1959 The American Medical Association Registry on Adverse Reactions recorded only 10 reports of leucopenia (fall in WBC count) and none in children.

1960-1964 18 cases reported (7 children). An increase in the import into USA of dipyrone from nil in 1958 to 18,879 lbs in 1962 was noticed.

1964 American Council of Drugs--Section One: adverse reactions: studied the case of Dipyrone (Analgin) and questioned the justification of continued use of this drug.

....3

1960 Great Britian and Canada revoked the licence of Dipyrone

1965 Australia and New Zealand issued an import ban on dipyrone

1974 Sweden revoked Dipyrone licence

1976 Norway revoked Dipyrone licence

1977 USA revoked Dipyrone licence
Japan banned free O.T.C. sale

1978 Ireland and Singapore revoked licence of dipyrone

1979 Denmark revoked licence of Dipyrone

1980-1984 An international study for agranulocytosis and aplastic anaemia was done in Europe--called the Boston Study, since coordination and data analysis was done at the Drug Epidemiology Unit at Boston. This was primarily financed by Hoechst, and the results published in the JAMA of Oct 1986.

1983 The Government of India banned the manufacture and sale of Amidopyrine

1986 Malaysia banned dipyrone.
FRG banned OTC sale
In Netherlands, Dipyrone use is only allowed for uncontrollable fever.

Following reports of anaphylactic shock, Italy, Egypt and Saudi Arabia have prohibited manufacture of injectible preparations.

3. The Issues

i. According to Hoechst, approximately 25 tonnes or 18.5 million doses of Novalgin are used world wide everyday. With most of the developed nations banning or restricting its use, it is obvious that it is sold mainly in third world countries.

The countries which have banned Dipyrone have been managing pain without Dipyrone by using equally effective and safe analgesics.

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ii. The 'Boston Study' generated a lot of controversy since Hoechst used the results even before publication for a misleading advertisement campaign showing the occurrence to be 1 per million. The hearing of the German Federal Health Office finally confirmed the assumption of 1 per 30,000 to 60,000 to be nearer the mark, or one tablet per 70,000 consumed could cause agranulocytosis based on this same study.

The limitations of this study are that--

a. it excludes all patients

i. who die of agranulocytosis without receiving medical aid;

ii. who die without having a white cell count; and

iii. who have undiagnosed agranulocytosis and recover from it.

b. it does not look into other side effects of dipyrone, like shock, fall in BP, Urticaria etc.

c. the data presented in the intermediate and final reports are inconsistant

d. whereas 400 cases of agranulocytosis were registered to assess risk properly, only 221 cases were analysed in the final report;

e. there is extreme variability in data between different countries and even within the same country; and

f. some data were seen to be clearly unreliable.

iii. The findings of the controversial 'Boston Study' is being utilised by Hoechst the largest manufacturer of Analgin for sales promotion in Germany, Eastern Bloc countries and the Third World. Unethical propaganda practices with different types of promotional literature in different countries is being practiced. Even claims of anti-spasmodic action which is not scientifically substantiated is being made. Any source of detailed scientific literature is virtually non-existant beyond the literature supplied by the drug companies.

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iv. Since 1985, Dipyrone (Analgin) has not found mention in any standard medical text books, except for naming it as a drug which can cause agranulocytosis.

v. Even in our country, medical students do not learn about analgin while doing their Pharmacology.

4. In India

i. In 1983, the Government of India banned the manufacture and sale of amidopyrine but not dipyrone. The Drugs Consultative Committee had recommended ban on FDCs of dipyrone also but this seems to have slipped from the banned list.

ii. The government is the largest manufacturer of dipyrone in this country.

iii. Analgin is among the largest selling analgesics in the country with sales figures accounting for Rs 70 million. There are approximately 200 formulations containing Analgin, including injectibles and drops for newborns and infants for colic.

iv. Analgin is available as OTC in spite of its being a Schedule H drug in our country and the attitude of the prescribing doctors as per a study (Lancet 86) was "if I prescribe it 30 times a day and it is available over the counter, it must be safe". In a field study (Lancet 86) it was seen that the pyrazolones made up the majority of both GP prescriptions and OTC sales of analgesics. One more of these drugs were given to over 50% of patients requesting an analgesic.

v. Drug action groups have initiated a campaign on Analgin especially at ACASH, Bombay, DAF-West Bengal and AIDAN, New Delhi.

vi. Analgin induced agranulocytosis does occur in India, especially if one looks for it systematically as a Bombay haematologist BC Mehta has done. He reports 12-15 cases of agranulocytosis a year, of which 10-12 are caused by Dipyrone or Dipyrone containing drugs. Even by the risk estimation of the Boston Study, in India, one person develops analgin induced agranulocytosis per day by other reasonable estimates, it could be 15 times this figure.

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5. Wider Issues

Developing countries like ours are ill placed to afford expensive and useless health care products and definitely not the frankly dangerous ones.

We have unsophisticated consumers and poorly developed regulatory and advisory systems--this is fertile ground for pharmaceutical companies to indulge in unacceptable practices.

The vast majority of rural doctors working in professional isolation have no access to independent information on drugs they prescribe. Here, the representative of the pharmaceutical company who is ill-informed himself and paid by commission on drug sales becomes an ideal tool to promote the interests of the Pharmaceutical company.

Thus, it appears that the consumer is at the mercy of drug manufacturers. Other than an appeal to the Food and Drugs Administration the Central Government and the MRTP Commission the consumer is virtually without recourse to any independent body such as the judiciary. The JJ Hospital Commission (Lentin Commission) enquiry reveals the ineffectiveness of these agencies. The Consumer Protection Act of 1986 is expected to offer some hope.

In effect only a public outcry by the consumer can force voluntary withdrawal by or reform by drug companies.

--S P TEKUR, Community Health Cell
47/1 St Mark's Road, Bangalore 560001

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ANALGIN – A STUDY FOR DRUG A.C.F.K.

1. ANALGIN – THE DRUG

A class of chemicals called PYRAZOLONES have been used as medicines for over ninety years. Pyrazolones include drugs like ANTIPYRINE, AMINOPYRINE, PHENYL BUTAZONE, OXYPHENBUTAZONE, SULFINPYRAZONE, and a derivative of Aminopyrine called DIPYRONE or ANALGIN. The pyrazolones share similar pain-killing, fever-reducing, inflammation-reducing properties, and also similar toxic properties.* They are rapidly absorbed in the stomach and intestine and spread in various tissues of the body in proportion to their water content. While 30 to 40% of the drug is altered in the liver and eliminated in the urine, 5% is eliminated unaltered. The fate of a significant fraction is not known.

Clinically, Analgin reduces fever in some rare diseases like Hodgkins disease and Periarteritis nodosa, where salicylates (Aspirins) are not completely effective, otherwise

The range of actions of pyrazolones is similar to that of salicylates (Aspirins) except in reducing fever in diseases like Hodgkins disease and Periarteritis nodosa, where aspirins are not completely effective.

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* Analgin being more water soluble is amenable to use in injections as well as in liquid oral preparations (for children).

has been variously estimated from 0.01% to 0.86%. If infection occurs now, it starts as a sore throat of sudden onset, high fever & prostration, which even on proper treatment carries a mortality of 20 to 50%.

The other adverse effects of Analgin documented in a study are, Skin rashes [redacted]%, Dyspepsia [redacted]%, Fever [redacted]%, Anaphylactic shock [redacted] and Bronchospasm [redacted]. Analgin can aggravate a bleeding tendency and produces a serious ~~hypothermia~~ fall in body temperature when given along with Chlorpromazine. ~~He~~ Liver cancer in mice has also been reported by Tappaniz.

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because, Pyrazolones were introduced in the pre-Thalidomide era when registration was easy.

HISTORY & PRESENT STATUS.

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1922 - Agranulocytosis was first described by

1922 - Dipyrone or Analgin was introd. by HOECHST. W. SCHULZ *

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Between 1955-59 - The American Medical Association

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Registry on Adverse Reactions recorded only 10 reports of Leucopenia (fall in W.B.C. count), and none in children.

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1979 - Denmark "

1986 - Malaysia banned dipyrone.

1986 - Fed Rep of Germany banned OTC sale. In Netherlands, dipyrone use is only allowed for uncontrollable fever.

~~Since 1985, Dipyrone has not found mention in any standard medical text book, except for ~~mentioning~~ naming it as a drug which can produce ~~a fatal~~ agranulocytosis. Even in our country, Medical students do not learn about this drug in the past few years during their study of Pharmac. Any source of detailed scientific literature is virtually non-existent beyond the literature supplied by the concerned drug companies.~~

The Pharma-campaign of BUKO, a network of more than 200 Development Action Groups in West Germany is fighting since 1980 against the harm and waste produced by the irrational marketing by Multinational companies, esp. HOECHST. BUKO is the co-founder of HAI (Health Action International) a network of some 50 groups in more than 38 countries worldwide.

1980 to 84 - An International Study for Agranulocytosis and Aplastic Anaemia was done in Europe - called the Boston Study since co-ordination & data analysis was done at the Drug epidemiology unit at Boston. This was primarily financed by HOECHST, and the results published in the JAMA of Oct '86.

Following reports of anaphylactic shock, Italy, Egypt and Saudi Arabia have prohibited manufacture of injectable preparations

1983 - The G.O.I. banned the manuf. and sale of Amidopyrine ~~...~~ ~~by the Drugs~~ consultative committee ~~...~~ FDCs of Analg

July 1980 - An International Study for Agranulocytosis and Aplastic Anaemia was started, ~~[illegible]~~ for a time span of 4 years, with co-ordination and data analysis done at the Drug Epidemiology Unit at Boston. This was the 'Boston study', whose results were published in the JAMA of Oct '86. This study was ~~[illegible]~~ financed by Hoechst

The issue (2)

- The 'Boston Study' generated a lot of controversy, since Hoechst used the results even before publication for a misleading advertisement campaign showing the occurrence to be 1 per million. The Hearing of the German federal Health Office finally confirmed the assumption of 1 per 30,000 to 60,000 to be nearer the mark, or, one tablet per 70,000 consumed could cause agranulocytosis based on this same study.

The limitations of this study are, that

(1) it excludes all patients
   - a) who die of agranulocytosis without receiving medical aid.
   - b) who die without having a white cell count, and
   - c) who have undiagnosed agranulocytosis and recover from it.

(2) the study does not look into other side effects of Dipyrone, like shock, fall in B.P., Urticaria, etc.

(3) the data presented in the intermediate and final reports are inconsistent.

(4) whereas 400 cases of agranulocytosis were reqd. to assess risk properly, only 221 cases were analysed in the final report, and

(5) there is extreme variability in data between diff countries and even within the same country.

(6) some data were seen to be clearly unreliable.

THE ISSUES !

(1) According to HOECHST, approx. 18·5 million 25 tons or doses of Novalgin are used world wide everyday. With most of the developed nations banning or restricting its use, it is obvious that it is sold mainly in 3rd world countries.

(2) The countries which have banned Dipyrone have been managing pain without Dipyrone by using equally effective and safe analgesics.

(3) (Same as below.) ~~3~~ Unethical propaganda practices with different types of promotional literature in different countries is being ~~followed by Hoechst, who is the largest manufacturer of Analgin~~ practiced. Even claims of anti-spasmodic action which is not scientifically substantiated is being made. ~~~~ contd---

(3) The F.D.A of U.S.A. regards that "true risk assoc. ε this drug far outweigh any benefit derived from its use, including use in Hodgkin's and similar malignant diseases.

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~~~~ → contd next para.

(6) Any source of detailed scientific literature is virtually non-existent beyond the literature supplied by the drug companies.

(3) Same as The findings of the controversial 'Boston study' is being utilized by Hoechst (Largest manufacturer of Analgin) for sale promotion in Germany, Eastern Bloc countries & the third world.
~~~~

4 IN INDIA

(1) 1983, the G.O.I. banned the manuf. & sale of Amidopyrine but not dipyrone. The Drugs consultative committee had recommended ban on FDCs of dipyrone also, but this seems to have slipped from the banned list.

(2) The Govt. is the largest manufacturer of Dipyrone in this country.

(3) Analgin's sales figures accounting for Rs 70 million, among the largest selling analgesics in the country with.

(~~4~~) ~~In a Bombay survey in 1985, 29% of the 256 analgesics prescribed contained Dipyrone.~~

Contd

(3) There are approx. 200 formulations containing Analgin, including injectables, and drops for newborns and infants for colic.

(6) Even now, ~~HOECHST promotes Analgin in Germany the Eastern Bloc and third world using the~~ controversial ~~finding~~ of the IARAS study.

(4) Analgin is available OTC inspite of its being a schedule H drug in India, our country, and the attitude of the prescribing doctors as per a study (Lancet 86) of over Metro practitioners is that if it is over the counter, it must be safe. ~~was, "if I prescribe it 30 times a day and it is available as available so easily, it must be safe."~~ ---(4)

(6) Drug action groups have initiated a campaign on Analgin, espec in Bombay, Calcutta at ACASH Bombay, DAF WB and AIDAN New Delhi

(5) Analgin induced agranulocytosis does occur in India, esp if one looks for it systematically as a Bombay haematologist B.C. Mehta has done. He reports 12-15 cases of granulocytosis a year, of which 10-12 are caused by Dipyrone or Dipyrone containg drugs. Even by the risk estimate of the Boston study, in India, one person develops Analgin induced agranulocytosis per day. By other reasonable estimates, it could be 15 times this figure

(4) In a field study ~~of~~ ~~in Indian~~ published in (Lancet '86), it was seen that the pyrazolones made up the majority of both G.P prescriptions & OTC sales of Analgesics. One of more of these drugs were given to over 50% of patients requesting an analgesic.

5 WIDER ISSUES.

Developing countries like ours are ill placed to afford expensive and useless health care products, and definitely not the frankly dangerous ones.

We have unsophisticated consumers and poorly developed regulatory and advisory systems. - this is fertile grounds for pharmaceutical companies to indulge in unacceptable practices.

The vast majority of rural doctors working in professional isolation have no access to independant information on drugs they prescribe. Here, the rep. of the pharmaceutical co. who is ill-informed himself and paid by commission on drug sales becomes an ideal tool to promote ~~drugs~~ & the interests of the Pharmac. co.

Thus, it appears that the consumer ~~is left~~ is at the mercy of drug manufacturers. Other than an appeal to the Food & Drugs Administration, the Central Govt., and the MRTP Commission, the consumer is virtually without recourse to any independant body such as the judiciary. The J.J. Hospital commission (Iyengar Commission) enquiry reveals the ineffectiveness of these agencies. The Consumer Protection Act of 1986 is expected to offer some hope.

In effect, only a public outcry by the consumer can force voluntary withdrawal by or reform by drug companies.

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2. Reviews of Medical Pharmacology - Meyers, Jawetz, Goldfien, 6th Ed. 1978.
3. Agranulocytosis induced by Dipyrone, a Hazardous Antipyretic and Analgesic. - Charles M. Hingsley Jr. JAMA, 21 Sep 84.
4. Risks of Agranulocytosis and Aplastic Anaemia — A first Report of the International Agranulocytosis and Aplastic Anaemia Study — JAMA. 03 Oct 86.
5. Analgin - pain killers or man killers? - Indian Express 24 Oct 87.
6. Why Analgin should be banned - a bit of history - Anant Phadke.
7. Counterfact on Analgin (An untold story) - Arun Gadkar, Anil Pilgaon Kar. Drugs, Disease, Doctor Vol 3. No. 4 1988
8. Dipyrone, Hoechst and the Boston study. MFC Bulletin Dec 86 - Wilbert Bannenberg.
9. Drug marketing in the Third World : Beneath the cosmetic reforms. - Lancet 07 Jun 86 - TRISHA GREENHALGH.
10. Dangerous and Inappropriate drugs - Lancet 28 Jun 86 M.J.S. Langman.
11. A BUKO Campaign - A DRUG CAMPAIGN NEWSLETTER mfc Rational Drug Policy Cell 1985
12. The Hoechst Medical Bulletin - Issue no. 8.

guru
guru

Document 1

TI Lack of direct interaction of metamyzole with the brain opiate receptors of rats.

AU Popova Y

AU Staneva-Stoycheva D

AD Institute of Physiology, Bulgarian Academy of Sciences

AB In earlier studies (Ivanov, Staneva-Stoycheva, 1984) we have found an inhibitory effect of metamyzole on the contractile responses of electrically stimulated guinea pig ileum and mouse vas deferens, which was naloxone-sensitive. In the present study, an attempt is made to clarify whether these pharmacologic effects of metamyzole are due to direct interaction with opiate receptors. The method of partial displacement of /3H/-naloxone to the opiate receptors in rat brain membranes was used. It was found that in the wide concentration range tested (10(-5) 10(-9) M), metamyzole did not compete with /3H/-naloxone for the opiate receptor sites. The biochemical study has shown that the presynaptic opiate receptors are not involved in the presynaptic effects of metamyzole, established in earlier studies.

SO Acta Physiol Pharmacol Bulg 1989;15 (1):...

Document 2

TI [Importance of endogenous opioid peptides in the effect of analgin (metamizole) and verapamil]

AU Vlaskovska M

AU Surcheva S

AU Ovcharov R

AB The effects of a non-narcotic analgetic methamizole and the calcium channel blocker verapamil on carrageenan hyperalgesia, release of beta-endorphin and synthesis of prostaglandin E2 (PGE2) were studied. It was found that a combined administration of analgin and verapamil prolonged the analgesic effect. Analgin stimulated release of beta-endorphin with the maximum coinciding in time with the peak of the analgesic effect. Against the background of the action of calcium ionophore A 23187 the combination of analgin with verapamil inhibited PGE2 synthesis more distinctly. The combination of these pharmacological agents is suggested to exert the effect both at different levels, central and peripheral, and on various cellular mechanisms involved in pain modulation.

SO Farmakol Toksikol 1989 May-Jun;52 (3):25-9

Document 3

TI [Study of the effect of analgeton on the release of beta-endorphin and its effect on chronic hyperalgesia]

AU Vlaskovska M

AU Krushkov I

AB The effect of the combined preparation analgeton and its components--analgin (metamizol, noramidopyrindimethansulfonate) and aminton (2-amino-4-methyl-pyridinphosphate) was studied on the release of beta-endorphin and its influence on chronic hyperalgesia. Experiments were carried out in vivo and in vitro on white rats and it was established that analgin, aminton and analgeton stimulated the release of beta-endorphin, affecting various regulatory levels. Analgeton in contrast to analgin showed longer analgetic effect in animals with chronic hyperalgesia (adjuvant arthritis of white rats). Possibilities for pharmacological control of chronic pain by influencing the levels of endogenous opioids are discussed.

SO Eksp Med Morfol 1989;28 (3):14-21

Document 4
TI [An evaluation of the efficacy of treating rheumatoid arthritis with preparations for local use]
AU Abdullaeva GK
AU Shakimova BSh
AB Assessment was made of the efficacy of local therapy of rheumatoid arthritis patients with dimexide during a double blind method of investigation. The articular index, duration of constraint in the morning and the strength of the hand were taken as the leading criteria for objective assessment of the drug efficacy. Applications of a 50% solution of dimethylsulforoxide give a statistically significant favourable effect as compared to the conventional physiotherapeutic methods of treatment: ultrasound and phonophoresis with analgin. Addition of analgin to a 50% solution of dimethylsulforoxide intensifies its antiphlogistic and analgesic properties.
SO Revmatologiia (Mosk) 1989 Oct-Dec; (4):35-9

Document 5
TI [Thresholds of the electrical excitability of the pulp in various groups of teeth and their changes under the influence of analgin, amidopyrine and diazepam]
AU Moroz BT
AU Ignatov IuD
AU Kalinin VI
AB Pulp electric excitability thresholds in different teeth groups and their changes under effects of analgin, amidopyrin and diasepam were studied using electro-odontometry in 58 patients and in experimental recordings of neuronal activity in rostral part of trigeminal complex under electrostimulation of molar and fang teeth. Baseline thresholds of pulp stimulation proved different in anterior teeth group and premolar/ molar group. Analgetic drugs used had more pronounced effect in cases of molar pulp stimulation.
SO Stomatologiia (Mosk) 1989 Sep-Oct;68 (5):30-2

Document 6
TI [The activation of specific type-III glucocorticoid receptors by pyrazolone series preparations]
AU Golikov PP
AU Nikolaeva NIu
AU Kladiev AA
AB Experiments were conducted on intact and adrenalectomized male Wistar rats (weighing 180-200 g) with labelled corticosterone of high specific activity to study the effect of analgin and aminopyrine on the level of type-III glucocorticoid receptors in the liver. Analgin and aminopyrine in doses of 10(-2) and 10(-3) increase the specific binding of labelled corticosterone by type-III glucocorticoid receptors of the hepatic cytosol and by blood plasma transcortin in modelled experiments. The effect of the agents depends on the dose. Intravenous administration of 140 mg/100 g of analgin to intact rats and intraperitoneal injection of an equal dose of analgin to adrenalectomized rats also increases the specific binding of labelled corticosterone by type-III glucocorticoid receptors of the hepatic cytosol. The importance of the revealed effect of agents of the pyrazolone series in stress regulation is discussed.
SO Patol Fiziol Eksp Ter 1989 Jul-Aug; (4):19-22

Document 7
TI [The effect of cholinergic agents on the analgesic effect of nonnarcotic analgesics]
AU Stets VR
AU Slivko SF
AB The effect of cholinergic agents on the analgetic effect of analgin (pyrazoline derivative) and chemical compounds (quinazoline and triazole derivatives) has been studied in experiments on white mice using a "hot plateo technique. It has been found that an M-cholinomimetic pilocarpine decreases pain sensitivity and enhances

of other agents. LD50 of LAS was similar to that of analgin and ASA. LAS toxicity was significantly less than that of amidopyrine. Bioavailability of ASA at intramuscular administration to rabbits was close to that at intravenous injection and significantly higher as compared with intragastric administration.
SO Farmakol Toksikol 1988 Sep-Oct;51 (5):78-82

Document 16
TI Analgin, the killer [letter]
AU Mathur SL
AU Bhargava CS
SO J Assoc Physicians India 1988 Aug;36 (8):523

Document 17
TI A comparative study of ibuprofen with paracetamol versus oxyphenbutazone with analgin combination in ophthalmic practice.
AU Roy IS
AU Das A
AU Roy M
SO Indian J Ophthalmol 1988 Jan-Mar;36 (1):37-40

Document 18
TI [Complex treatment of dental plexalgia using physiotherapeutic methods]
AU Sharov MN
AU Grechko VE
AU Puzin MN
AB A total of 66 patients with dental plexalgia have been examined and treated at the neurological dentistry department. A multiple-modality scheme for the treatment of this condition is suggested, whose basic methods are physiotherapeutic ones: longitudinal physiotherapy, diadynamic currents with a narcotic mixture, trimecain or lydase + analgin electrophoresis. The treatment was effective in the majority of patients.
SO Zh Nevropatol Psikhiatr 1988;88 (2):57-60

Document 19
TI [Effect of multiple peroral use of analgin on the liver monooxygenase system in the rat]
AU Koleva M
AU Kaloianova F
AU Dobreva V
AU Mitova S
AB Analgin given repeatedly per os in dose 15 mg/kg to white male rats, causes changes in some indices of the liver NADPH-dependent mono-oxygenase system. At the end of the first month a decrease in the quantity of the microsomal protein was established as well as increase of the cytochrome's content P-450 and b5. The frequencies of cytochrome P-450-dependent biotransformations of substrates aminopyrine and aniline are also of different directions. At the end of the sixth month, because of multiple drug application all these indices are in the limits of the control values. A change in the catalytic features of cytochrome P-450, is established, which is expressed mainly by strongly decreased affinity to the substrates of first type. The Michaelis's constant Km for substrate aminopyrine depends on the duration of analgin introduction and increases up to 300% towards the control at the end of the sixth month.
SO Probl Khig 1987;12 :87-92

amounts was done by a colorimetric method after extraction with dichloromethane.
SO Arch Geschwulstforsch 1989;59 (2):79-84

Document 14
TI [Analgesic activity of pymadine]
AU Mitsov V
AU Bantutova I
AB The analgesic effect of 4-aminopyridine (pymadine) was studied in experiments on rats and mice at thermal and chemical pain stimulation. Pymadine (1, 3 and 5 mg/kg) exerted the analgesic effect when administered alone and concomitantly with analgin and morphine at chemical pain stimulation. During thermal pain stimulation pymadine had the analgesic effect only at dosage of 5 mg/kg and potentiated the action of morphine given in doses of 3 and 5 mg/kg. The same doses of pymadine failed to influence changes in pain reaction induced by analgin at thermic pain stimulation.
SO Farmakol Toksikol 1988 Jul-Aug;51 (4):32-4

Document 15
TI [Analgesic action and pharmacokinetics of lysine acetylsalicylate administered intramuscularly]
AU Libina VV
AU Cha ika LA
AU Kosheleva LP
AU Khadzha i IaI
AU Pichugin VV
AB The analgesic effect, acute toxicity and pharmacokinetics of lysine acetylsalicylate (LAS) , a water-soluble salt of acetylsalicylic acid (ASA) were studied as compared with a 50% solution of analgin and a 4% solution of amidopyrine at intramuscular administration and ASA administered intragastrically. During inflammation-induced pain in

all three analgetics. Relative sensitivity of homozygotes increased with the elevation of drugs concentration. The data obtained demonstrate the mutagenicity of the analgetics tested for Drosophila.
SO Genetika 1990 May;26 (5):856-62

Document 21
TI [The effect of analgin on glucocorticoid receptors]
AU Golikov PP
AU Nikolaeva NIu
AB Scatchard's analysis was used to examine the specific binding of 3H-acetonide of triamcinolone (3H-AT) by Type II glucocorticoid receptors of cytosol from the liver of Wistar rats weighing 180-200 g. It was found that analgin in concentrations of 5.0 and 10.0 mM inhibited the density of glucocorticoid receptors and increase the dissociate rate constant of 3H-AT from the receptor and decreased 3H-AT elimination half-life from the receptor. Analgin in concentrations of 0.04, 0.08, 0.16, 0.31, 0.62, 1.25, and 2.50 mM lowered the association constant of the 3H-AT-receptor complex in proportion to the increase of analgin concentrations. Analgin was found to have uncompetitive effects followed by inhibition of the density of Type II glucocorticoid receptors.
SO Eksp Klin Farmakol 1993 Jul-Aug;56 (4):41-4

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(metamizol, Analgin) is mainly metabolized by phenobarbital-inducible cytochrome P-450 (P-450PB) . We investigated the elimination of caffeine by the use of plasma concentration curves (HPLC) and the elimination of metamizol by spectrophotometric determination of the metabolites in urine in 10 healthy young males, in 10 healthy young females using no OL-steroids and in 10 healthy young females using OC-steroids. No influence of sex on the microsomal drug metabolism activity of these two drugs has been observed. There was a significantly decreased microsomal drug metabolism of both drugs in females under hormonal contraception. We conclude that OC-steroids decrease the demethylation activity of both P-450MC and P-450PB.

SO Pharmazie 1985 Jan;40 (1):50-2

Document 26

TI [Effect of nontoxic inhibitors on the nitrosation of drugs under conditions simulating the human stomach]

AU Ziebarth D

AU Schramm T

AB The influence of sulphamic acid, sulfanilamide, p-aminosalicylic acid and ascorbic acid on the nitrosation behaviour of Analgin (active agent: noramidopyrinmethane sulfonate) was investigated in the pH range between 1.2 and 6.0 under simulated conditions of the human stomach. Using a colorimetric measuring method, the three last-mentioned compounds proved suitable as nitrosation inhibitors; preference should be given to ascorbic acid because of its better inhibitory capacity in the very weakly acidic pH range. Sulphamic acid is inadequate because it stimulates nitrosation in this pH range. The distinct inhibitory action of ascorbic acid was verified under simulated conditions of the human stomach in further 9 drugs undergoing nitrosation at different rates, which contain the active agents: aminophenazone, clomipramine, imipramine, desipramine, ampicilline, oxacilline, phenoxymethylpenicilline, athambutole or piperazine. Despite the use of high doses of ascorbic acid, no complete inhibition of nitrosation could be achieved in the majority of drugs investigated.

SO Arch Geschwulstforsch 1985;55 (2):81-91

Document 27

TI [Acute kidney failure and acute toxic cholestatic hepatitis caused by a large amount of analgin]

AU Monov A

AU Chernev K

AU Penkova S

AU Boshnakova Ts

SO Vutr Boles 1985;24 (1):133-6

Document 8

TI [The diagnosis of drug hypersensitivity]

AU Badina AK

AB The author revealed an increase of dienic conjugates in 391 patients under the effect of drugs in patients with drug intolerance and a study is also presented in 46 patients with good tolerance to drugs. It is shown that the dienic test has an information value as to intolerance of penicillin, streptomycin, tetraolean, analgin, novocaine and vitamin B1.

SO Vrach Delo 1990 Dec; (12):46-9

Document 9

TI [Sensitivity of larvae of Drosophila melanogaster mutant mus(2)201G1 to various analgesics]

AU Mikheev VS

AU Imianitov EN

AB Sensitivity of larvae from mutagen-sensitive mus(2)201G1 mutant of Drosophila melanogaster to analgin, amidopyrine and antipyrine (4-64 mkmol/ ml of medium) was studied. Relative frequency of flies homozygous for this mutation after combined development of homozygous and heterozygous flies in the medium with the analgetic was used as a criterion for larval sensitivity. It is shown that sensitivity of

pyrazolone-induced urticaria were marked by chronic diseases requiring the prolonged and frequent intake of the analgesics, pyrazolone derivatives. The allergological examination of the 35 patients with pyrazolone-induced urticaria showed that only one of the patients had pollenosis, 6 patients had IgG-mediated reactions to egg protein and one patient to penicillin. For specific diagnosis of drug allergy use was made of the natural leukocyte migration test in vivo according to A. D. Ado. The test appeared positive with analgin in all the 35 patients suffering from pyrazolone-induced urticaria. It represents a simple and accessible method for specific diagnosis of drug allergy both in inpatients and in those visiting allergological rooms at the polyclinics. The immunological examination made with the aid of the histograms demonstrated an appreciable reduction in the content of D-phagocytosing neutrophils. The latter fact might explain the presence of multiple chronic foci of infection in patients with pyrazolone-induced urticaria. Such patients manifested a decrease in C3 that might be related to immediate activation of the alternative pathway of complement by pyrazolone derivatives.

SO Ter Arkh 1986;58 (10):76-8

Document 22

TI [Indomethacin in the treatment of ureteral colic caused by calculi]

AU Bick C

AU Suckow B

AU Heil G

AB Experiences are reported in the therapy of recurrent colics caused by ureteroliths. In 41 patients an initial treatment with indomethacin suppositories was performed which led to a removal of the colics in 37 patients. A comparative group of 46 patients was conventionally treated by means of an injection therapy of analgin/papaverin. In order to achieve painlessness, on a average 10 to 15 injections were necessary during the hospital treatment. The importance of the indomethacin therapy described lies in the possible self-application by the patient as well as in the avoidance of recurrent colics, frequent consultations of emergency physicians and hospitalisations.

SO Z Urol Nephrol 1986 Dec;79 (12):705-8

Document 23

TI [Transplacental passage of sodium salicylate and analgin in the last trimester of pregnancy and labor]

AU Todorov S

AU Todorov I

AU Kiutukchiev B

AU Khadzhiev A

AU Ruseva S

SO Akush Ginekol (Sofiia) 1985;24 (4):30-4

Document 24

TI [Combined poisoning with phenobarbital and analgin complicating metastatic lesions of the adrenals from cancer of the lung]

AU Naumov VN

AU Krasnova RR

AU Galkina VS

SO Sud Med Ekspert 1985 Jul-Sep;28 (3):54-5

Document 25

TI [Determination of caffeine and metamizole elimination in men and women with and without hormonal contraceptives as an in vivo method for characterization of various cytochrome P-450 subspecies]

AU Simon HU

AU Ortweiler W

AU Siegert C

AU Splinter FK

AU Balogh A

AU Traeger AM

AB Caffeine is mainly metabolized by 3-methylcholanthrene-inducible [illegible] P-450 (P-450MC) and paramidopyrine-methanol[illegible]

the quantity of the microsomal protein was established as well as increase of the cytochrome's content P-450 and b5. The frequencies of cytochrome P-450-dependent biotransformations of substrates aminopyrine and aniline are also of different directions. At the end of the sixth month, because of multiple drug application all these indices are in the limits of the control values. A change in the catalytic features of cytochrome P-450, is established, which is expressed mainly by strongly decreased affinity to the substrates of first type. The Michaelis's constant Km for substrate aminopyrine depends on the duration of analgin introduction and increases up to 300% towards the control at the end of the sixth month.

SO Probl Khig 1987;12 :87-92

Document 20

TI [Dynamic aspects of mineral metabolism in dry cows, puerperants and calves]

AU Planski B

AU Abrashev N

AB It is investigated the calcium, phosphorous and magnesium homeostasis in cows in the dry period, cows in child-birth and calves in connection with the diarrhea in the newborn during the neonatal period, with the respiratory syndrome in the growing up, with the sterility in heifers, with the stillborn, with estrous and postestrous metrorrhagia. It was ascertained a close dependence in the value of Ca, P and Mg in the different physiologic groups of a given farm. It was ascertained that the newborn from mothers with lower serum values of Ca of 2.5 mmol/l, P of 1.8 mmol/l and Mg of 0.70 mmol/l suffer from diarrhea, endotoxic shock, tetany etc. during the neonatal period. Hypocalcemia is registered in the calves with a respiratory syndrome (2.20 mmol/l), sterile heifers (2.39 mmol/l). In all cases is ascertained hypophosphorosis and hypomagnesemia especially in the calves with a respiratory syndrome (P = 1.24 and Mg = 0.46 mmol/l), cows with a still born calves (P = 0.92 and Mg = 0.54 mmol/ l) with metrorrhagia (P = 0.93 and Mg = 0.71 mmol/l). The diagnostic value of the product Ca X P X Mg is discussed. A reversible relationship between them is ascertain In comparison with the ideal in which Ca X P X Mg is 11.11 and the ratio--1.09, in the above mentioned diseases the product decreases and the ratio increases. The differences are graded which shows their mutual origin. It was established experimentally that the addition with a medical aim to the ration of the green pea-oats and green rye during spring and summer, such as oats in winter for the pregnant cows has a decisive effect on the living of the newborn. It was ascertained as well that in extra situations a component containing, calcium gluconate, magnesium sulphate, sodium salicylate, analgin, B1 vitamin, vitamin C, sodium phosphate, glucose and sodium chlorate (if necessary sulfathiazole) injected s.c. 5 times to the pregnant cows 15-5 days before childbirth has a positive effect on the new-born calves.

SO Vet Med Nauki 1987;24 (10):48-57

Document 21

TI [Clinico-immunological and allergological characteristics of urticaria caused by pyrazolone derivatives]

AU Poroshina IuA

AU Luss LV

AU Gervazieva VG

AB The authors describe the results of clinical, allergological and immunological examination of 35 patients with urticaria caused by pyrazolone derivatives. Clinically, the patients with

...algesic action and pharmacokinetics of lysine acetylsalicylate administered intramuscularly]

AU Libina VV
AU Cha ika LA
AU Kosheleva LP
AU Khadzha i IaI
AU Pichugin VV

AB The analgesic effect, acute toxicity and pharmacokinetics of lysine acetylsalicylate (LAS), a water-soluble salt of acetylsalicylic acid (ASA) were studied as compared with a 50% solution of analgin and a 4% solution of amidopyrine at intramuscular administration and ASA administered intragastrically. During inflammation-induced pain in rats LAS exerts a pronounced analgesic effect exceeding the activity of other agents. LD50 of LAS was similar to that of analgin and ASA. LAS toxicity was significantly less than that of amidopyrine. Bioavailability of ASA at intramuscular administration to rabbits was comparable with that at intravenous injection and significantly higher as

SO Farmakol Toksikol 1988 Sep-Oct;51 (5):78-82

AU [illegible] killer [letter]

AB [illegible]

TI [Determination of micro-amount of dipyrone with a piezoelectric detector]
AU Yao SZ
AU Tan SL
AU Nie LH
AB A new method for the determination of dipyrone (analgin) using a piezoelectric quartz crystal as detector has been proposed. An iodine-potassium iodide solution is added to the sample and the frequency shift of the crystal immersed in the sample solution with respect to the blank is directly proportional to the concentration of dipyrone over a range from 2 x 10(-7) to 3 x 10(-6) mol/L at pH 3.5-6.5 according to the equation C (mol/L) = 6.85 x 10(-9) delta F (Hz) . No significant interferences were caused by commonly met inorganic substances, amino acids and a number of other organic substances. The method has been suggested for determining dipyrone at ppm level and in micro-samples of mg or microliters level.
SO Yao Hsueh Hsueh Pao 1989;24 (2):122-6

Document 12
TI [Effect of analgin on glucocorticoid receptors of the liver]
AU Golikov PP
AU Kladiev AA
AU Nikolaeva NIu
AB The experiments were performed on intact and phlogogenically exposed male Wistar rats (weighing 180-210 g). Glucocorticoid receptors were determined in a high-rate cytosol of the liver by using 3H-acetonide triamcinolone. Inflammation was induced by subplantar administration of formalin. In the model experiments, analgin (10(-2) M) decreased the level of glucocorticoid receptors in the rat liver cytosol. In a dose of 250 mg/kg intraperitoneally, analgin after 90 min decreased the liver content of glucocorticoid receptors and blood plasma concentrations of corticosterone in intact and phlogogenically exposed rats. The mechanism of the decrease of the content of glucocorticoid receptors in the liver and blood plasma concentrations of corticosterone in analgin-treated animals is discussed.
SO Farmakol Toksikol 1989 Jul-Aug;52 (4):52-5

Document 13
TI [Effect of various forms of diet on the nitrosation of sodium metamizole (analgin tablets) under simulated conditions of the human stomach]
AU Ziebarth D
AU Kuldm ae LA
AD Zentralinstitut f ur Krebsforschung der Akademie der Wissenschaften der DDR, Robert-R ossle-Institut, Berlin-Buch.
AB The influence of a simple and a more complex diet on the formation of nitrosometamizole from sodium metamizole (analgin tablets) under simulated human gastric conditions was estimated with extremely different nitrite concentrations. Only with the complex diet and only with low nitrite concentrations, the formation of nitrosometamizole was distinctly lowered. The quantitative estimation of the formed amounts was done by a colorimetric method after extraction with dichloromethane.
SO Arch Geschwulstforsch 1989;59 (2):79-84

Document 14
TI [Analgesic activity of pymadine]
AU Mitsov V
AU Bantutova I
AB The analgesic effect of 4-aminopyridine (pymadine) was studied in experiments on rats and mice at thermal and chemical pain stimulation. Pymadine (1, 3 and 5 mg/kg) exerted the analgesic effect when administered alone and concomitantly with analgin and morphine at chemical pain stimulation. During thermal pain stimulation pymadine had the analgesic effect only at dosage of 5 mg/kg and potentiated the action of morphine given in doses of 3 and 5 mg/kg. The same doses of pymadine failed to influence changes in pain reaction induced by analgin at thermic pain stimulation.
SO Farmakol Toksikol 1989 Jul-Aug;52 (4):32-4

especially that of quinazoline and triazole derivatives. At high doses (10 mg/ kg) pilocarpine increases drastically the toxicity of analgin. Contrastingly, an M-cholinoblocker atropine does not affect considerably the pain sensitivity, however blocks completely the analgetic effect of all the drugs studied. The role of cholinergic mechanisms in the maintenance of pain sensitivity level and the onset of the analgetic effect of non-narcotic analgesics as well as the clinical value of the data obtained are discussed.
SO Anesteziol Reanimatol 1989 Nov-Dec; (6):24-7

Document 8
TI [Postoperative analgesia by endolymphatic administration of analgin]
AU Pyshkin SA
AU Tkachev SV
AU Reznik IuI
AU Bashtan LP
AU Malaia VV
SO Klin Khir 1989; (12):55-6

Document 9
TI Prescription audit of under six children living in periurban areas.
AU Prakash O
AU Mathur GP
AU Singh YD
AU Kushwaha KP
AB One hundred and seventy two children were prescribed, in 212 episodes of illness, antimicrobial agents (28.4%), followed by antidiarrheals (10.9%) , nutritional products (9.4%), analgesics (7.5%) and steroids (6.8%) . Ampicillin (22.7%) and cotrimoxazole (12.7%) were the most commonly prescribed antimicrobials. Tetracyclines, which are not indicated in children below 8 years, were used in 7.1% of total exposures of chemotherapeutic agents. Penicillin, a comparatively safe and useful drug, was used only in 4.5% exposures. Analgin and hydroxyquinolines were used frequently. Corticosteroids were used for simple ailments like diarrhea, fever and jaundice. ORS was used in only 13.9% episodes of diarrhea. Adverse drug reactions were noted in 30 (17.4%) cases and death in 6 (3.5%) cases. The average cost per prescription for neonates was Rs 32.43 and for a child was Rs 30.65. Weight of the children was not taken prior to prescribing drugs. There is need for prescription audit as there is high consumption rate of drugs, with overuse of antimicrobial and nutritional products, and misuse of steroids.
SO Indian Pediatr 1989 Sep;26 (9):900-4

Document 10
TI [Changes in thymocyte DNA template activity under the effect of agents acting on the central nervous system]
AU Golikov PP
AU Nikolaeva NIu
AU Alekseeva EA
AB The authors studied the effect of phrenolon, amitriptyline, piracetam, caffeine (concentrations of 10(-7), 10(-6), 10(-5) M), analgin, and amidopyrine (concentrations of 2.5 10(-7), 2.5 10(-6), 2.5 10(-5) M) on the matrix activity of thymocyte DNA. The thymocyte suspension was derived from the thymus of adrenalectomized male rats. The matrix activity of the thymocyte DNA was evaluated according to the ability of these cells to reduce the incorporation of 3H-uridine into thymocyte mRNA. Biosynthesis of thymocyte mRNA reduced under the effect of phrenolon, amitriptyline, and analgin. When phrenolon, amitriptyline, analgin, and amidopyrine were administered together with triamcinolone acetonide, the inhibiting effect of the latter agent on the matrix activity of thymocyte DNA increased; piracetam and caffeine failed to produce such an effect. The practical significance of the obtained results in the clinic or emergencies is discussed.
SO Patol Fiziol Eksp Ter 1989 May-Jun; (3):18-21

TABLE - 1

B-COMPLEX TABLETS

Brand Name	Elemental iron in mg	Vit.B1 mg.	Vit B2 mg.	Vit B6 mg.	Vit B12 mcg.	Vit FA mg.	Nic-acid mg.	Cap. panto. mg.	Vit.C mg.	Price in paise for equivalent dose (based on price in june 81.
Complex B Glaxo	-	3	1	0.5	5	-	30	1	-	-1 tablet of 4 paise.
Libex	-	3.3	3.3	1	1.66	.33	30	-	50	14.6 (1T = 44 paise)
Becozyme -C	-	3	3	2	2	-	10	5	40	9.3 (1T = 46.5 paise)
Cobadex Forte	-	5	2.5	1	1	. 5	7	1	20	4.45 (1 T=44.5 paise)
Boplex	-	10	2.5	0.5	-	-	25	3	-	1 T = 4.25
				B-COMPLEX INJECTIONS						
Complex B glaxo	-	5	.5	1.5	5	-	25	2.5	-	0.5 ml : 17
Bejectal	-	5	1	2.5	-	-	0.75	2.5	-	0.5 ml : 34

TABLE - 2

MULTIVITAMIN TABLETS

Brand name	Vit.B1 mg.	Vit.B2 mg.	Vit.B6 mg.	Vit.B12 mcg	Vit. FA mg.	Nic. acid	Ca-Panto. mg.	Vit A I.U.	Vit. D IU mg.	Vit. C mg.	Minerals	Iron solt mg	Price in paise for equivalent dose. (based on prices in June 1981).
Vimgran	3	3	1	2	0.1	20	5	5000	500	50	-	-	13.5 = 1 Tablet
Vitaminets Forte	10	2	3	1	-	10	10	4000	400	50	-	-	18 = 1 Tablet
Multivitaplex Forte	2.5	2.5	.5	1.25	.25	25	-	5000	3.7	38	-	-	10 (39.5 = 1T)
MULTI VITAMIN SYRUP													
Multivita-plex	3.5	2.7	1	-	-	20	-	5000	1000	50	-	-	5 ml = 38.65
Becadex	1.5	1.2	-	2.5	-	10	-	3000	500	40	-	-	5 ml = 21.45
Visyneral	1.5	0.6	1	2	-	10	2	3000	1000	50	-	-	5 ml = 32.75
MULTI VITAMIN DROPS													
ABCDEC	1	0.4	1	-	-	5	2	5000	1000	50	-	-	0.6 ml. = 14.2
Vitamin M drops	1.5	1.2	.5	-	-	10	-	5000	1000	50	Mn K 17.27 Zn		0.6 ml = 17.08
Alvite	10	2	1	-	-	20	-	5000	500	30	-	-	55
Vi-Syneral	5	0.5	1.5	-	-	10	-	5000	400	25	-	-	48

TABLE NO.3

IRON WITH MULTIVITAMIN TABLETS

Brand Name	Vit B1 mg.	Vit B2 mg.	Vit B6 mg.	Vit B12 mcg.	FA Folic acid mg.	Vit C mg	Cap panto. mg	Nic acid mg	Elemental Iron in mg.	Price in paise for equivalent dose(based on prices in June 81
Iberol	1	1	0.5	4.6	.33	25	1	5	52.5	6.3(1 tablet costs 19 paise.)
Exifol	2	2	1	100	5	50	3	10	45	1 T = 59
Fesovit	2	2	1	-	-	50	-	15	45	1 T = 60.3
Fersolate + Complex B Glaxo	3	1	.5	5	-	-	1	30	60	1 T = 7.5 paise.
IRON WITH FOLIC ACID AND VIT B 12										
Ferplus				66 5	1	150			66	1 tablet = 34.3
Femitinic				10	1	150			66	1 T = 41.8
Macrafolin with iron				10	1	-			66	1 T = 6.5
Autrin				9	1.2	90			70	20.76(1T = 34.6) (34.6 x 3/5)
Rediplex				10	1	100			68.6	21.3 (1T = 32) (32x 2/3)
Fersolate									66	3.5
Imforon F12				668	3.2				66.4	154
Uniferon F12				66.4	3.2				66.4	76

(Tables prepared by Nitin Sane, Pune).

The following materials are available with Community Health Cell (47/1 St Mark's Road, Bangalore 560001) for reference:

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Rational Drug use

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Drugs are the hallmark of Modern Medicine. The 'healing professions' throughout the ages have always used 'natural' or 'synthetic' products for their medicinal value, to treat various common ailments of people. Drugs, however, have never in the past dominated the medical scene as they have done in the second half of this century. Today, the *'pill for every ill'* culture is well established. It has ensured that we are probably the most 'drugged generation' of all times. Not a very healthy thought!

Throughout the centuries, philosophers, social activists and concerned doctors have warned against the dangers and problems of overuse or misuse of drugs by doctors and the people.

The Indian Situation

The Indian Council of Medical Research and the Indian Council of Social Sciences Research set up a joint study group to study the health situation in India and evolve an alternative strategy for our commitment to 'Health for All by 2000 AD." This high powered expert committee had some very interesting things to say about the present situation of drugs and prescribing practices, in their Report published in 1981. (1)

★ "There is now an over-production of drugs (often very costly) meant for the rich and well-to-do while the drugs needed by the poor people (and these must be cheap) are not adequately available. This skewed pattern of drug production is in keeping with our inequitous social structure which stresses the production of luxury goods for the rich at the cost of the basic needs of the poor....

★ One of the most distressing aspects of the present health situation in India is the habit of doctors to over-prescribe glamorous and costly drugs with limited medical potential. It is also unfortunate that the drug producers always try to push doctors into using their products by all means - fair or foul. These basic facts are more responsible for distortions in drug production and consumption than anything else.

★ Eternal vigilance is required to ensure that the health care system does not get medicalised, that the doctor-drug-producer axis does not exploit the people and that the abundance of drugs does not become a vested interest in ill-health."

These warnings are a serious indictment of the medical profession and the drug industry in the country. It confirms the growing evidence that drugs are being pushed on an unsuspecting public by devious methods which masquerade as 'sales promotion' of drug companies and 'professional prescribing practice' by doctors and health workers. All of us who are committed to 'Health' need to be concerned about this situation. The promotion of a *'Rational Drug Use'* by the medical profession and health workers and ultimately by the consumers - the patient community and the public, is an important item on the agenda of HEALTH ACTION.

"There are two types of physicians - those who promote life and attack diseases; those who promote diseases and attack life."

- Charaka Samhita

Irrational Drug Use - some dimensions

To understand the principles of Rational Drug Use, one needs to first identify and appreciate the elements of irrationality in the present situation. A spate of reports appearing in our newspapers and periodicals highlight these elements. Of all of them, however, the report of the recent 'Lentin Commission' and its shocking findings are the most telling.

Irrationality in drug use arises out of three sets of factors:

A Irrationality in drug production, marketing and availability

B Irrationality in prescribing practices of doctors and health workers

C Irrationality in drug use by the consumer public.

All these taken together result in the situation we find ourselves today.

A Irrationality in drug production, marketing and availability

★ **Industrial Policy**
Drug policy continues to be part of the industrial policy and not part of the health policy. Industrial growth and profit margins determine the policy and not health needs of the people.

★ **Over abundance**
There is a plethora of drugs produced in the country. The Hathi Committee recommended 116 as essential and the WHO says 200 are necessary. At present there are over 60,000 formulations in the country.

★ **Quality of drugs**
Twenty percent of the drugs available in the country are substandard and spurious. Many are adulterated. Many are old and being sold after the expiry dates are over.

Turmeric powder in tetracycline capsules and poor quality intravenous fluids have been reported. The substandard 'glycerol' in J J Hospital highlighted by the Lentin report is another example.

★ **Unwanted Drugs**
The formulations available include the following:

i **Banned drugs:** Drugs which have been banned in many countries such as Lomotil and Clioquinol.

ii **Irrational combinations:** Formulations which have combinations that are antagonistic or irrational. The Hathi Committee had suggested weeding out of atleast 23 such groups of preparations. These were finally banned by a gazette notification in July 1983 but continue to be available.

iii **Hazardous or Bannable drugs:** Hazardous drugs which should not be available without prescription or adequate medical supervision. Preparations containing analgin, oxyphenbutazone and cortico-steroids are the commonest examples (Refer A to Z of Drug use - page 31)

iv Drugs promoted for indications that are not clinically proven or are potentially dangerous, eg., promotion of EP Forte combinations for pregnancy testing and induction of abortion even when there is well documented evidence that risk of foetal deformity is increased by the use of these preparations. (now banned since 1988 June 30.)

v **Costly Drugs:** Drugs which are inflated in cost by inclusion of costly, additional, often unnecessary ingredients or by cosmetic embellishments in manufacture and packaging. Tonics and high protein foods especially baby foods are good examples.

★ **Wrong Priorities**
There is over-production of unimportant drugs or drugs for the rich while drugs for some common health problems are in short supply. Tonics, vitamins, hormone preparations and high protein substitutes are being produced in wasteful abundance while drugs for leprosy and tuberculosis (two major public health problems) are produced at one third and one fourth of actual requirements. Similarly Vitamin A and many vaccines urgently required for child care programmes are frequently in short supply.

★ **Over-the-counter sales**
Sale of drugs over-the-counter without doctor's prescriptions or the necessary statutory checks are not at all uncommon. This results from inadequate drug legislation and even more inadequate drug controls. Over-the-counter unauthorised sales of prescription drugs, which now-a-days do not even have the precautionary product information make the situation even more hazardous.

"The physician who sets about to treat a disease without knowing anything about it is to be punished even if he is a qualified physician; if he does not give proper treatment, he is to be punished more severely; and if by his treatment the vital functions of the patient are impaired, he must be punished most severely."

- Koutilya Arthashastra

★ **Escalating Prices**
Price control policies have been both inadequate and ineffective and hence the cost of drugs has been constantly escalating. With liberalization policies of the present government this is bound to increase further. The purchasing power of majority of our patients is limited. With increasing prices, patients are forced to buy only part of a prescription or go in for sub-standard alternatives promoted by the drug shops.

B Irrational Drug Prescribing

Doctors, nurses and health workers often prescribe or administer drugs irrationally. The types of irrational drug prescribing has been classified as follows: (4)

Type of irrational drug use	Occurs if a drug is prescribed when:
1 Extravagant prescribing	- A less expensive drug would provide comparable efficacy and safety
	- symptomatic treatment of mild conditions divert funds from treating serious illness
	- a brand name is used where less expensive equivalents are available.
2 Over-prescribing	- the drug is not needed
	- the dose is too large
	- the treatment period is too long
	- the quantity dispensed is too great for the current course of treatment
3 Incorrect prescribing	- the drug is given for an incorrect diagnosis
	- the wrong drug is selected for the indication
	- the prescription is prepared improperly
	- adjustments are not made for co-existing medical, genetic, environmental or other factors.
4 Multiple prescribing	- two or more medications are used when one or two would achieve virtually the same effect.

- several related conditions are treated when treatment of the primary condition will improve or cure the other conditions.

5 Under prescribing
- needed medications are not prescribed
- dosage is inadequate
- length of treatment is too brief.

How does such prescribing take place?

There are many background factors which lead to such prescribing practices.

a Inadequate training

Doctors, nurses, pharmacists and health workers may be inadequately trained in the use of drugs. The training may be theoretical and not geared to the practice of prescribing in the real life situation. Technical minutiae may be stressed at the cost of information on cost, social context and hazard.

b Inadequate continuing education

The doctor, pharmacist, nurse or health workers in field practice are inadequately supported by a process of continuing education by their professional associations and training institutions. Once graduation is over, there is little opportunity to refresh one's knowledge of drugs and medical matters through unbiased sources of information.

☆c Unethical medical advertising

Medical advertising of drugs has been more often than not, found to be full of unproven claims of efficacy. In addition, promotional literature all over the world by the same company for the same drug has been found to be vastly different. Facts are withheld or modified. Statistics are used in a biased manner. Drug company sponsored misinformation is not uncommon.

Drug:	**Tetracycline** (antibiotic used against various infections; Lederle Laboratories)	
	Caution against use	*Adverse reaction publicized*
U.S.A.	By infants, children; during pregnancy; liver or kidney impairement (latter can be fatal) or if overly sensitive to light.	Vomiting, diarrhoea, nausea, stomach upset, rashes, kidney poisoning, can poison fetus.
Mexico	By infants, children, during pregnancy or if overly sensitive to light.	vomiting, diarrhoea, nausea, stomach upset.
Brazil	By infants, children, during pregnancy	vomiting, nausea, stomach upset, rashes
Argentina	None	None

Courtesy: Mother Jones, USA

"Physicians prescribe medicine of which they know little, to cure diseases of which they know less, in human beings of which they know nothing."

- Voltaire
18th century

d Prescribing for prestige/ power

Doctors especially often prescribe extravagantly as a sign of 'prestige' and 'power'. In India people often consider a good doctor to be one who gives a long, costly prescription, in keeping with his list of degrees. Many doctors succumb to this cultural status symbol. A vicious cycle is maintained thereby.

e Busy outpatients

Many of our institutions are understaffed especially those run by the government. The queues at the out-patient clinic are long and there is a heavy rush. Lack of time to make a good clinical judgement often results in an irrational prescription including drugs for all eventualities.

f Inducements by medical companies

Misinformation is not the only method by which doctors are made to prescribe irrationally by medical companies. Sales promotion includes a host of practices such as unethical trade discounts, bribes, gifts, sponsorship for conferences and travel. The commercial proposition induces many doctors to prescribe unethically.

g Unauthorised prescribing

Health workers and practitioners of other non-allopathic systems of medicine are often by virtue of their training unauthorised to prescribe all the drugs in the medical armamentarium. Health workers may be trained to prescribe only a few drugs. Too often they get a larger number of drugs and dispense them to get the community's approval and get greater prestige. Many traditional medicine practitioners, dispense allopathic drugs with little background training or knowledge.

h Drugs as a substitute for caring

Drugs have become a symbol of the new medical culture, where

treatment is primarily drug oriented and all other aspects of 'caring' and nursing of the patient are relegated to the back ground. When simple home remedies like hot water gargles and nursing procedures can provide relief to many symptoms of the patients, doctors prefer to prescribe symptomatic drugs instead, thus increasing drug consumption irrationally.

i Commercialisation of the medical profession

There was a time not so long ago when the doctors' profession was a vocation. Aspirants to the profession saw service to the sick and ailing as more important than the financial rewards they would get, if at all, from their grateful patients. Today the situation has changed drastically. Parents are willing to pay lakhs to get their children into medical school. No such investment would be made if the returns were not equally rewarding. Aspirants today therefore see medicine as a business investment. In such a social ethos 'irrational prescribing' for pecuniary benefits would not at all be frowned upon. In fact it may even be seen as a stepping stone to success.

c Drug use by Consumer Public - irrational dimensions

i Self-medication

Medication by patients themselves is not an uncommon problem. Either they are too poor to consult doctors or because of the easy availability of drugs they medicate themselves, encouraged by the pharmacists, advertisements, peer group information or advise of family members. A survey conducted by the National Institute of Nutrition in the twin cities of Hyderabad and Secunderabad covering 10 percent of the 330 retail Pharmaceutical shops showed that self-medication rate was an alarming 46 percent.

ii Use of unutilized drugs

It is a very common habit among the consumer public to take a medicine, not as the doctor has directed but just enough to feel better. This is often the case with antibiotics and particularly for children. Unused medicine is kept in the home pharmacy and given to one or other of the children or family member who gets the same symptoms, next. Unused or unutilized portion of prescribed medicine is often kept beyond expiry date. If proper storage precautions are not taken, it may also get denatured. Use of such medicines is a major cause of untoward reactions.

"The incidence of disease cannot be manipulated and so increased sales volume must depend at least in part on the use of drugs unrelated to their utility or need or in other words improperly prescribed. Human frailty can be manipulated and exploited and this is fertile ground for anyone who wishes to increase profits."

- Kefauver Committee Hearing on Drugs, USA

iii Inadequate labelling or storage of medicine

Medicines prescribed by doctors are often inadequately labelled by the dispensing pharmacist. Storage instructions are not very clearly explained to the patient. The medicine cupboard is often a source of irrational drug use. Children may have access to it and this may lead to accidential poisoning.

iv Peer-group exchange

Consumers of drugs often advise relatives, friends and neighbours about the benefits a particular prescribed drug has given them. They are advised to take these drugs for what is thought to be a similar complaint or disease. This peer group exchange is often the cause of much irrational drug use by the lay public.

v Status-symbol drugs

Capsules, injections, and tonics have become status symbol drugs. They are thought to be more effective and also being costlier are considered to be of greater prestige value. Patients often demand or pressurise their doctors to prescribe one or more of these and doctors often comply with the request to retain the patient and family in their practice.

vi Multiple consultations

Patients often go to many doctors seeking quick relief of their symptoms. The doctors are not often aware that consultation with them is one of many such concurrent events. Generalists and Specialists may both be consulted. Practitioners of different systems may be consulted simultaneously. Different medicines given by different doctors are then consumed with the hope of getting relief. When relief does occur it is not easy to decide which medicine brought it about.

Multiple prescriptions then become a way of life when symptoms recur. Many drugs may potentiate one another. Others may work at cross purposes. When the consultation is of plural systems the confusion is worse.

vii Inadequate Consumer Awareness

Probably one of the key factors for irrational drug use by

consumers is the absence of awareness of drug use, misuse and the effects of overuse. Consumer education is next to absent in India. Due to loopholes in the existing laws, precautionary product information is not supplied with the medical products. The media, the medical profession, the educational system and the social welfare agencies concentrate on the misuse of psychotropic substances and drug abuse. Misuse, overuse or abuse of commonly prescribed drugs is not considered to be an adequately serious problem for consumer education. The problem is further compounded by a large illiterate population and the need of such efforts to be in multiple languages when they do get organized.

Rational Drug use - Principles

The irrationalities and predisposing factors promoting unsafe drug use in our country have been described. The challenge that faces all of us today is: How to counter this phenomena? Health for All by 2000 AD would be an empty slogan if we did not join and participate actively in a consumer and professional movement to tackle the 'irrational drug use' problem. In the absence of prompt efforts in this direction, we would probably arrive at a situation-over abundant drugs and ill-health for all by 2000 AD.

What could be our prescription for action?

A thorough understanding of the situation would lead us to appreciate the following principles. (3)

Rational Drug Use

★ means practice of socially conscious, relevant and scientifically sound medicine

★ emphasises the selective use of drugs based on
- essentiality
- efficacy
- safety
- easy availability
- low cost
- ease of administration
- adequate quality
- preferably of indigenous production

★ recognises the concept of essential drugs and the concept of graded lists for different levels of health personnel

★ recognises the non-role of drugs in certain conditions, the role of alternative systems of medicine in some other conditions and recognises the overall limitations of allopathic medicine in our economic, social and cultural context.

★ accepts a conscious decision to boycott certain drugs which are hazardous or bannable or banned and use all others only when they are really needed.

★ means prescription with awareness, to avoid as far as possible iatrogenesis (doctor induced disease) which includes -
- drug induced problems
- drug interactions
- adverse drug reactions
- emerging drug resistance

★ recognises the rights of health personnel and consumers to unbiased drug information and its effective communication.

★ understands the role of drugs in the emerging health movement.

For all of us concerned about the increasing *medicalising of health* action and the *'over abundance of drugs'* becoming a *'vested interest in ill health'* **there is a phenomenal challenge in making the above principles of Rational Drug use**
- **common knowledge**
- **common practice**
- **commom commitment.**

In conclusion, drugs have allayed pain and suffering over the centuries. They have helped many live more comfortable, productive and meaningful lives. All of us committed to the health movement must ensure that drugs should continue to play their limited but useful role in medical service. However, the use of drugs knowingly and unknowingly, to make profit out of human health must stop.

And it will only if
Governments;
drug industries;
planners;
health professionals;
medical colleges;
pharmacy colleges;
nursing colleges;
drug controllers;
pharmacists;
journalists and media persons;
teachers and educators;
social development activists;
consumer groups;
and
the public
commit themselves to promoting a Rational Drug Use.

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Part I

DRUG POLICIES - GOVERNMENT OF INDIA 1978

The Hathi Committee Report

The Government of India set up on February 8, 1974 a Committee under the Chairmanship of Shri Jaiskhlal Hathi and other members of parliament along with various officials and non-officials, to enquire into the various facts of the drug Industry in India.

The Hathi Committee submitted its report to Government in April 1975. The report was laid on the tables of both houses of Parliament in May 1975. After several inter ministeral discussion, and discussions with representatives of drug industry, the views of the cabinet committee was put in February 1977, but could not be considered. Final decisions of Government based on the reports were made on 29th March 1978.

Broad objects of the New Drug Policy

(i) To develop self-reliance in drug technology;

(ii) To provide a leadership role of the public sector;

(iii) To aim at quick self-sufficiency in the output of drugs with a view to reduce the quantum of imports;

(iv) To foster and encourage the growth of the Indian sector;

(v) To ensure that the drugs are available in abundance in the country to meet the health needs of our people;

(vi) To make drugs available at reasonable prices;

(vii) To keep a careful watch on the quality of production and prevent adulteration and mal-practices;

(viii) To offer special incentives to firms which are engaged in Research and Development; and

(ix) To provide other parameters to control, regulate and rejuvenate this industry as a whole, with particular reference to containing and channelizing the activity of foreign companies in accord with national objectives and priorities.

The new drug policy aims at promoting the Indian Drug Industry. At first the Hathi Committee also recommended that the Multinationals should be taken up by Government, however, since this was a drastic change, this view was not adopted. If nationalisation takes place Government would also take over Indian companies above a certain size. Certain stringencies were, however, laid down with regard to foreign companies like Small Scale Sector will be a prohibited area, formulation licences for foreign companies will be given only if they are linked with the production of ohigh technology bulk drugs from the basic stage.

Another important policy adopted was with regard to Brand names. Brand names shall be abolished in the first instance in respect of the following five drugs ;-

...2

Rational Drug use

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★ **Quality of drugs**
Twenty percent of the drugs available in the country are substandard and spurious. Many are adulterated. Many are sold and being sold after the expiry dates are over.

Turmeric powder with tetracycline capsules and poor quality intravenous fluids have been reported. The substandard 'glycerol' in J J Hospital highlighted by the Lentin report is another example.

★ **Unwanted Drugs**
The formulations available include the following:

i **Banned drugs:** Drugs which have been banned in many countries such as Lomotil and Clioquinol.

ii **Irrational combinations:** Formulations which have combinations that are antagonistic or irrational. The Hathi Committee had suggested weeding out of atleast 23 such groups of preparations. These were finally banned by a gazette notification in July 1983 but continue to be available.

iii **Hazardous or Bannable drugs:** Hazardous drugs which should not be available without prescription or adequate medical supervision. Preparations containing analgin, oxyphenbutazone and cortico-steroids are the commonest examples (Refer A to Z of Drug use - page 31)

iv Drugs promoted for indications that are not clinically proven or are potentially dangerous, eg., promotion of EP Forte combinations for pregnancy testing and induction of abortion even when there is well documented evidence that risk of foetal deformity is increased by the use of these preparations. (now banned since 1988 June 30.)

v **Costly Drugs:** Drugs which are inflated in cost by inclusion of costly, additional, often unnecessary ingredients or by cosmetic embellishments in manufacture and packaging. Tonics and high protein foods especially baby foods are good examples.

★ **Wrong Priorities**
There is over-production of unimportant drugs or drugs for the rich while drugs for some common health problems are in short supply. Tonics, vitamins, hormone preparations and high protein substitutes are being produced in wasteful abundance while drugs for leprosy and tuberculosis (two major public health problems) are produced at one third and one fourth of actual requirements. Similarly Vitamin A and many vaccines urgently required for child care programmes are frequently in short supply.

★ **Over-the-counter sales**
Sale of drugs over-the-counter without doctor's prescriptions or the necessary statutory checks are not at all uncommon. This results from inadequate drug legislation and even more inadequate drug controls. Over-the-counter unauthorised sales of prescription drugs, which now-a-days do not even have the precautionary product information make the situation even more hazardous.

"The physician who sets about to treat a disease without knowing anything about it is to be punished even if he is a qualified physician; if he does not give proper treatment, he is to be punished more severely; and if by his treatment the vital functions of the patient are impaired, he must be punished most severely."

- Koutilya Arthashastra

★ **Escalating Prices**
Price control policies have been both inadequate and ineffective and hence the cost of drugs has been constantly escalating. With liberalization policies of the present government this is bound to increase further. The purchasing power of majority of our patients is limited. With increasing prices, patients are forced to buy only part of a prescription or go in for sub-standard alternatives promoted by the drug shops.

B Irrational Drug Prescribing

Doctors, nurses and health workers often prescribe or administer drugs irrationally. The types of irrational drug prescribing has been classified as follows: (4)

Type of irrational drug use	Occurs if a drug is prescribed when:
1 Extravagant prescribing	- A less expensive drug would provide comparable efficacy and safety - symptomatic treatment of mild conditions divert funds from treating serious illness - a brand name is used where less expensive equivalents are available.
2 Over-prescribing	- the drug is not needed - the dose is too large - the treatment period is too long - the quantity dispensed is too great for the current course of treatment
3 Incorrect prescribing	- the drug is given for an incorrect diagnosis - the wrong drug is selected for the indication - the prescription is prepared improperly - adjustments are not made for co-existing medical, genetic, environmental or other factors.
4 Multiple prescribing	- two or more medications are used when one or two would achieve virtually the same effect.

- several related conditions are treated when treatment of the primary condition will improve or cure the other conditions.

5 Under prescribing
- needed medications are not prescribed
- dosage is inadequate
- length of treatment is too brief.

How does such prescribing take place?

There are many background factors which lead to such prescribing practices.

a Inadequate training

Doctors, nurses, pharmacists and health workers may be inadequately trained in the use of drugs. The training may be theoretical and not geared to the practice of prescribing in the real life situation. Technical minutiae may be stressed at the cost of information on cost, social context and hazard.

b Inadequate continuing education

The doctor, pharmacist, nurse or health workers in field practice are inadequately supported by a process of continuing education by their professional associations and training institutions. Once graduation is over, there is little opportunity to refresh one's knowledge of drugs and medical matters through unbiased sources of information.

c Unethical medical advertising

Medical advertising of drugs has been more often than not, found to be full of unproven claims of efficacy. In addition, promotional literature all over the world by the same company for the same drug has been found to be vastly different. Facts are withheld or modified. Statistics are used in a biased manner. Drug company sponsored misinformation is not uncommon.

Drug:	**Tetracycline** (antibiotic used against various infections; Lederle Laboratories)	
	Caution against use	*Adverse reaction publicized*
U.S.A.	By infants, children, during pregnancy; liver or kidney impairement (latter can be fatal) or if overly sensitive to light.	Vomiting, diarrhoea, nausea, stomach upset, rashes, kidney poisoning, can poison fetus.
Mexico	By infants, children, during pregnancy or if overly sensitive to light.	vomiting, diarrhoea, nausea, stomach upset.
Brazil	By infants, children, during pregnancy	vomiting, nausea, stomach upset, rashes
Argentina	None	None

Courtesy: Mother Jones, USA

"Physicians prescribe medicine of which they know little, to cure diseases of which they know less, in human beings of which they know nothing."

- Voltaire
18th century

d Prescribing for prestige/ power

Doctors especially often prescribe extravagantly as a sign of 'prestige' and 'power'. In India people often consider a good doctor to be one who gives a long, costly prescription, in keeping with his list of degrees. Many doctors succumb to this cultural status symbol. A vicious cycle is maintained thereby.

e Busy outpatients

Many of our institutions are understaffed especially those run by the government. The queues at the out-patient clinic are long and there is a heavy rush. Lack of time to make a good clinical judgement often results in an irrational prescription including drugs for all eventualities.

f Inducements by medical companies

Misinformation is not the only method by which doctors are made to prescribe irrationally by medical companies. Sales promotion includes a host of practices such as unethical trade discounts, bribes, gifts, sponsorship for conferences and travel. The commercial proposition induces many doctors to prescribe unethically.

g Unauthorised prescribing

Health workers and practitioners of other non-allopathic systems of medicine are often by virtue of their training unauthorised to prescribe all the drugs in the medical armamentarium. Health workers may be trained to prescribe only a few drugs. Too often they get a larger number of drugs and dispense them to get the community's approval and get greater prestige. Many traditional medicine practitioners, dispense allopathic drugs with little background training or knowledge.

h Drugs as a substitute for caring

Drugs have become a symbol of the new medical culture, where

treatment is primarily drug oriented and all other aspects of 'caring' and nursing of the patient are relegated to the back ground. When simple home remedies like hot water gargles and nursing procedures can provide relief to many symptoms of the patients, doctors prefer to prescribe symptomatic drugs instead, thus increasing drug consumption irrationally.

i Commercialisation of the medical profession

There was a time not so long ago when the doctors' profession was a vocation. Aspirants to the profession saw service to the sick and ailing as more important than the financial rewards they would get, if at all, from their grateful patients. Today the situation has changed drastically. Parents are willing to pay lakhs to get their children into medical school. No such investment would be made if the returns were not equally rewarding. Aspirants today therefore see medicine as a business investment. In such a social ethos 'irrational prescribing' for pecuniary benefits would not at all be frowned upon. In fact it may even be seen as a stepping stone to success.

c Drug use by Consumer Public - irrational dimensions

i Self-medication

Medication by patients themselves is not an uncommon problem. Either they are too poor to consult doctors or because of the easy availability of drugs they medicate themselves, encouraged by the pharmacists, advertisements, peer group information or advise of family members. A survey conducted by the National Institute of Nutrition in the twin cities of Hyderabad and Secunderabad covering 10 percent of the 330 retail Pharmaceutical shops showed that self-medication rate was an alarming 46 percent.

ii Use of unutilized drugs

It is a very common habit among the consumer public to take a medicine, not as the doctor has directed but just enough to feel better. This is often the case with antibiotics and particularly for children. Unused medicine is kept in the home pharmacy and given to one or other of the children or family member who gets the same symptoms, next. Unused or unutilized portion of prescribed medicine is often kept beyond expiry date. If proper storage precautions are not taken, it may also get denatured. Use of such medicines is a major cause of untoward reactions.

"The incidence of disease cannot be manipulated and so increased sales volume must depend at least in part on the use of drugs unrelated to their utility or need or in other words improperly prescribed. Human frailty can be manipulated and exploited and this is fertile ground for anyone who wishes to increase profits."

- Kefauver Committee Hearing on Drugs, USA

iii Inadequate labelling or storage of medicine

Medicines prescribed by doctors are often inadequately labelled by the dispensing pharmacist. Storage instructions are not very clearly explained to the patient. The medicine cupboard is often a source of irrational drug use. Children may have access to it and this may lead to accidential poisoning.

iv Peer-group exchange

Consumers of drugs often advise relatives, friends and neighbours about the benefits a particular prescribed drug has given them. They are advised to take these drugs for what is thought to be a similar complaint or disease. This peer group exchange is often the cause of much irrational drug use by the lay public.

v Status-symbol drugs

Capsules, injections, and tonics have become status symbol drugs. They are thought to be more effective and also being costlier are considered to be of greater prestige value. Patients often demand or pressurise their doctors to prescribe one or more of these and doctors often comply with the request to retain the patient and family in their practice.

vi Multiple consultations

Patients often go to many doctors seeking quick relief of their symptoms. The doctors are not often aware that consultation with them is one of many such concurrent events. Generalists and Specialists may both be consulted. Practitioners of different systems may be consulted simultaneously. Different medicines given by different doctors are then consumed with the hope of getting relief. When relief does occur it is not easy to decide which medicine brought it about.

Multiple prescriptions then become a way of life when symptoms recur. Many drugs may potentiate one another. Others may work at cross purposes. When the consultation is of plural systems the confusion is worse.

vii Inadequate Consumer Awareness

Probably one of the key factors for irrational drug use by

consumers is the absence of awareness of drug use, misuse and the effects of overuse. Consumer education is next to absent in India. Due to loopholes in the existing laws, precautionary product information is not supplied with the medical products. The media, the medical profession, the educational system and the social welfare agencies concentrate on the misuse of psychotropic substances and drug abuse. Misuse, overuse or abuse of commonly prescribed drugs is not considered to be an adequately serious problem for consumer education. The problem is further compounded by a large illiterate population and the need of such efforts to be in multiple languages when they do get organized.

Rational Drug use - Principles

The irrationalities and predisposing factors promoting unsafe drug use in our country have been described. The challenge that faces all of us today is: How to counter this phenomena? Health for All by 2000 AD would be an empty slogan if we did not join and participate actively in a consumer and professional movement to tackle the 'irrational drug use' problem. In the absence of prompt efforts in this direction, we would probably arrive at a situation-over abundant drugs and ill-health for all by 2000 AD.

What could be our prescription for action?

A thorough understanding of the situation would lead us to appreciate the following principles. (3)

Rational Drug Use

- ✯ means practice of socially conscious, relevant and scientifically sound medicine
- ✯ emphasises the selective use of drugs based on
  - essentiality
  - efficacy
  - safety
  - easy availability
  - low cost
  - ease of administration
  - adequate quality
  - preferably of indigenous production
- ★ recognises the concept of essential drugs and the concept of graded lists for different levels of health personnel
- ★ recognises the non-role of drugs in certain conditions, the role of alternative systems of medicine in some other conditions and recognises the overall limitations of allopathic medicine in our economic, social and cultural context.
- ★ accepts a conscious decision to boycott certain drugs which are hazardous or bannable or banned and use all others only when they are really needed.
- ★ means prescription with awareness, to avoid as far as possible iatrogenesis (doctor induced disease) which includes -
  - drug induced problems
  - drug interactions
  - adverse drug reactions
  - emerging drug resistance
- ★ recognises the rights of health personnel and consumers to unbiased drug information and its effective communication.
- ★ understands the role of drugs in the emerging health movement.

For all of us concerned about the increasing *medicalising of health* action and the *'over abundance of drugs'* becoming a *'vested interest in ill health'* **there is a phenomenal challenge in making the above principles of Rational Drug use**

- common knowledge
- common practice
- commom commitment.

In conclusion, drugs have allayed pain and suffering over the centuries. They have helped many live more comfortable, productive and meaningful lives. All of us committed to the health movement must ensure that drugs should continue to play their limited but useful role in medical service. However, the use of drugs knowingly and unknowingly, to make profit out of human health must stop.

And it will only if
Governments;
drug industries;
planners;
health professionals;
medical colleges;
pharmacy colleges;
nursing colleges;
drug controllers;
pharmacists;
journalists and media persons;
teachers and educators;
social development activists;
consumer groups;
and
the public
commit themselves to promoting a Rational Drug Use.

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Part I

DRUG POLICIES - GOVERNMENT OF INDIA 1978

The Hathi Committee Report

The Government of India set up on February 8, 1974 a Committee under the Chairmanship of Shri Jaiskhlal Hathi and other members of parliament along with various officials and non-officials, to enquire into the various facts of the drug Industry in India.

The Hathi Committee submitted its report to Government in April 1975. The report was laid on the tables of both houses of Parliament in May 1975. After several inter ministeral discussion, and discussions with representatives of drug industry, the views of the cabinet committee was put in February 1977, but could not be considered. Final decisions of Government based on the reports were made on 29th March 1978.

Broad objects of the New Drug Policy

(i) To develop self-reliance in drug technology;

(ii) To provide a leadership role of the public sector;

(iii) To aim at quick self-sufficiency in the output of drugs with a view to reduce the quantum of imports;

(iv) To foster and encourage the growth of the Indian sector;

(v) To ensure that the drugs are available in abundance in the country to meet the health needs of our people;

(vi) To make drugs available at reasonable prices;

(vii) To keep a careful watch on the quality of production and prevent adulteration and mal-practices;

(viii) To offer special incentives to firms which are engaged in Research and Development; and

(ix) To provide other parameters to control, regulate and rejuvenate this industry as a whole, with particular reference to containing and channelizing the activity of foreign companies in accord with national objectives and priorities.

The new drug policy aims at promoting the Indian Drug Industry. At first the Hathi Committee also recommended that the Multinationals should be taken up by Government, however, since this was a drastic change, this view was not adopted. If nationalisation takes place Government would also take over Indian companies above a certain size. Certain stringencies were, however, laid down with regard to foreign companies like Small Scale Sector will be a prohibited area, formulation licences for foreign companies will be given only if they are linked with the production of ohigh technology bulk drugs from the basic stage.

Another important policy adopted was with regard to Brand names. Brand names shall be abolished in the first instance in respect of the following five drugs ;-

...2

The Drug Industry in India—

What our experts say

The Industry

The total output of the industry increased hundredfold-from Rs. 100 million in 1947 to Rs. 10,500 million in 1978-79. This was due to expanded production, especially of an ever-increasing number of sophisticated drugs, and rising prices...

The drug industry has enjoyed a higher man-average profitability so that investment therein has increased substantially from Rs. 240 million in 1952 to Rs. 4,500 million in 1977.

There are about 125 large and medium factories and nearly 3, 000 small scale sector units engaged in this industry which provides employment to about 100,000 workers.

Pattern of Drug Production

There is now an overproduction of drugs (often very costly) meant for the rich and the well-to-do while the drugs needed by the poor people (and these must be cheap) are not adequately available. This skewed pattern of drug production is in keeping with our inequitous social structure which stresses the production of luxury goods for the rich at the cost of the basic needs of the poor.

Out of a total production of Rs. 700 crores in 1976, 25 percent is taken away by vitamins, tonics, health restoratives and enzyme digestants, mostly consumed by the relatively well-fed urban population. Twenty percent is covered by antibiotics, only 1.3 percent by sulphonamides (a very cheap and useful anti-infective) and 1.4 percent by anti-tuberculosis drugs...

Pattern of Prescribing

One of the most distressing aspects of the present health situation in India is the habit of doctors to over-prescribe glamorous and costly drugs with limited medical potential. It is also unfortunate that the drug producers always try to push doctors into using their products by all means—fair or foul. These basic facts are more responsible for distortions in drug production and consumption than anything else.

Structure of the Industry

The existing drug policy rightly emphasises the attainment of self-sufficiency in the production of drugs, in increasing the share of the Indian producers and in giving a more significant role to public sector.

The foreign companies account for about 40 percent of the total drug production in the country; their share in the production of basic drugs was about 28 percent and that in formulations, 44 percent (1978-79). This is still high.

Price Control

The drug prices are high and continue to rise. In some instances, Indian prices are even higher than the international ones.

Packaging increases the cost of drugs very greatly because the trend is to make it attractive and highly elegant and to add cosmetic embellishments to promote sales...

There may indeed be a glut of applications for the introduction of 'Me-too Drugs' which will not attract new legislation for another five years in regard to price control...

Genuine 'breakthrough' research has declined in recent times.

Existing prices of drugs including those of essential drugs of everyday use is highly inflated. For example, the cost of analgin sold over the counter is 30 times the cost of production.

Prices are often inflated by the use of brand names.

Very often, prolonged controversy over the price of a drug has resulted in stopping its production.

The bill for import of bulk drugs, intermediates, solvents etc., has jumped from Rs. 53.77 crores in 1976-77 to about Rs. 119 crores in 1979-80.

Quality Control

The standards prescribed are unrealistic... are mechanically copied from books.. and not uniformly enforced in all parts of the country.

Consumption of Drugs

At present the supplies of drugs to urban and rural institutions within the health care system is very uneven. In an urban hospital, for instance, the drug cost is Rs. 6 per patient per year while in a Primary Health Centre, it is about 40 paise per patient per year.

An Overview

We recognise the value and significance of drugs in the health care system. We fully support the policy that all the essential drugs should be produced in the country, preferably in the Indian sector, and that they should be made available to the people at reasonable prices. To realize these objectives, it is essential to lay down and vigorously implement a national drug policy which will ensure that the pattern of drug production in the country (barring drugs meant for export) should be geared to its actual needs. While the supply of drugs should be adequate, *eternal vigilance is required to ensure that the health care system does not get medicalized, that the doctor-drug-producer axis does not exploit the people, and that the 'abundance' of drugs does not become a vested interest in ill-health.*

Source :

Health for All—An alternative Strategy : report of a study group set up jointly by the Indian Council of Social Science Research (ICSSR) and the Indian Council of Medical Research (ICMR).

Misuse and overuse of medicines—Why ?

Some Reasons

1. **Big business** The production and marketing of modern medicines is one of the biggest, most profitable business in the world. Drug companies are continually inventing new products to increase their sales and profits. Some of these medicines are useful. But atleast 90% of medicine on the market today are unnecessary. Doctors prescribible them and people buy them, because the drug companies spend millions on advertising.

2. **False advertising** Especially in poor countries, much of the advertising, and even the information published in 'pharmaceutical indexes', is misleading or false. Information on dangerous side effects is often not included. Risky medicines are frequently recommended for illnesses less dangerous than the medicines. (For example chloramphenicol has often been advertised as a treatment for minor diarrhoea and respiratory infections).

3. **Dumping** Drug companies in wealthy countries sometimes produce medicines that do not sell well in their homelands. Or the use of certain medicines is restricted or prohibited because they have been proved unsafe. It is a common practice for drug companies to 'dump' these medicines on poor countries—often with a great deal of false advertising. For example, several years ago the U.S. government restricted the use of Lincocin (lincomycin) because it proved more dangerous, more costly, and generally less effective than penicillin. The following year, thanks to massive advertising, Lincocin became the best selling drug in Mexico!

4. **Lack of adequate controls.** Poor countries, especially, have inadequate laws controlling the production and sale of medicines. As a result, many poor countries sell up to 3 times as many different medicines as rich countries do. Most of these medicines are a waste of money. Many are completely unreasonable combinations of drugs, yet they are widely prescribed by doctors. For example, in both Latin America and Asia, a popular injectable medicine is tetracycline combined with chloramphenicol. This is a senseless combination because the two drugs are 'incompatible' and should never be used together.

5. **Bribes and corruption.** Drug companies in rich countries pay millions in bribes to officials in poor countries so that governments will buy their products. (A major US Pharmaceutical company recenty admitted to having spent millions of dollars on bribes to advance its products in poor countries).

6. **Sale of prescription medicines without prescriptions** This is common in many countries (partly because poor people cannot afford doctors' fees). Most people who 'self-medicate' try to use the medi-

cines well, so they follow the patterns set by doctors. Unfortunately, this often leads to incorrect use. For example, in Latin America atleast 95% of doctors, prescriptions for Vitamin B_{12} injections are among the most widely used self-prescribed medicines in Latin America—at a cost of millions to a people too poor to eat well!

7. **People not adequately informed.** Neither doctors nor the people are adequately informed about the correct use of medicines. Most doctors rely on the information given in misleading 'blurbs' supplied with sample medicines, while villagers who self-prescribe often receive no information at all. In Mexico, for example, upto 70% of prescription drugs are sold without prescription. Yet the packaging of these medicines generally contains no information about use, dosage, or risks.

8. **Health Workers not adequately informed** In spite of the tremendous amount of self-medication in most countries, many programs still do not teach health workers much about the use—or misuse—of commonly self-prescribed medicines. As a result, many health workers to meet popular demand, secretly purchase and administer a wide range of medicines they know little about.

9. **Use of medicine to gain prestige and power.** Another reason for medicine overuse is that many professionals use their ability to medicate as a sort of magic to make people grateful and dependent. This way they gain special privilege and power. In the same way. health workers may be tempted to give injections or expensive drugs when home remedies or kindly advice would cost less and do more good.

From Helping Health Workers Learn
—David werner and Bill Bower

This rare Himalayan herb will cure your headache. If it doesn't I'll give you a pill prepared by a famous multinational drug house.

Medication as a Substitute for Caring

Perhaps the biggest reason for over-use of medicines, however, is that doctors and health workers often find it easier to hand out medicine than to give the time and personal attention that people need.

About 4 out of 5 illnesses are *self limiting*. This means people get well whether they take medicine or not. **Most health problems can be better managed without medication. What often will help people most is friendly advice and understanding support.**

However, many doctors and health workers get into the habit of giving everyone medicine—for any and every problem they have. The less curable the problem, the more medicines they give!

At the same time, people have come to expect medicine every time they visit a doctor or health worker. They like to believe that "there is a medicine for everything". They are disappointed if the doctor or health worker does not give them any, even when medicines will do no good and the health worker carefully explains why.

So a 'vicious circle' results in which the doctor always gives medicine because the 'patient' always expects (or demands) it, because the doctor always gives it. **The prescribing of a medicine becomes both the symbol and the substitute for human caring**. This problem especially common in places where doctors, nurses, and health workers are over worked. The result is not only a costly overuse of medicine, but a failure to meet human needs on human terms.

—Helping Health Workers Learn
David Werner and Bill Bower.

"The physician who sets about to treat a disease without knowing anything about it is to be punished even if he is a qualified physician; if he does not give proper treatment, he is to be punished more severely, and if by his treatment the vital functions of the patient are impaired, he must be punished most severely."

—Koutilya Arthashastra

'If there are no side effects, this must be Argentina

DRUG COMPANY SPONSORED MISINFORMATION OF DOCTORS

In countries with less well-organized drug control mechanisms, studies have shown that the same drug manufactured by the same multinational company is sold for more indications.

with less contra-indications
less side effects

as compared to the information provided in U.S.A.

The following comparison of promotional literature for three drugs bears this out only too well.

Drug : **Tetracycline** (Antibiotic used against various infections; Lederle Loboratories)

	Caution Against Use	Adverse reactions publicized
U.S.A.	By infants, children; during pregnancy : Liver or kidney impairement (latter can be fatal) or if overly sensitive to light.	Vomiting, diarrhoea, nausea, stomach upset, rashes, kidney poisoning, can poison fetus.
Mexico	By infants, children; during pregnancy or if overly sensitive to light.	Vomiting, diarrhoea, nausea, stomach upset.
Brazil	By infants, children, during pregnancy.	Vomiting, nausea, stomach upset, rashes.
Argentina	None	None

Drug : **Ovulen** (birth control pills : GD Searle Co.) in US used for contraception only. In some Latin countries, Searle recommends it also for regulating menstrual cycles, premenstrual tension, menopausal problems.

	Caution against use	Adverse reactions publicized
U.S.A.	If patient has tendency to blood clot, liver dysfunction, abnormal vaginal bleeding, epilepsy, migrain, asthma, heart problem.	Nausea, loss of hair, nervousness, jaundice, high blood pressure, weight change, headaches.
Mexico	If patient has tendency to blood clot, liver dysfunction.	Nausea, weight change.
Brazil	If patient has tendency to blood clot	None

(*Contd. to page 30*)

(*Contd. from page 22*)

Argentina	If patient has tendency to blood clot.	None

Drug : **Imipramine** (Anti-depressant, Ciba Geigy) In U.S. used for depression only. In some Latin American countries, Ciba Geigy recommends it also for senility, pain and alcoholism

	Caution against use	Adverse reactions publicized
U.S.A.	If patient has heart disease, history of urinary retention, history of seizures, manic disorder or is on typhoid medication. Not recommended for children or during pregnancy.	Hypertension, stroke, stumbling, delusions, insomnia, numbness, dry mouth, blurred vision, constipation, itching, nausea, vomiting, loss of appetite, diarrhoea
Mexico	During first trimester of pregnancy	Dry mouth, constipation itching, sweating
Brazil	If patient has heart disease; not recommended for children or during pregnancy	None
Argentina	May exaggerate response to alcohol	None

(Taken from the Mother Jones, Courtesy—Health and Society, also mfc bulletin 73-4, Jan-Feb 1982).

The Crazy World of Tonics

Mukarram Bhagat

'Health' tonics are a craze with the affluent in the cities with their supposedly hectic, energy-consuming life-styles. Feeling tired? Pop a pill or gulp down a spoonful and it will keep you going (nobody knows where!)

The most commonly used tonics are multi-vitamin preparations with highly excessive quantities of vitamins.

Incremin C, the famous growth tonic with the Giraffe logo, contains an important amino acid lysine which the human body cannot synthesise by itself. However, a teaspoon of Incremin contains only about 300 milligrams of lysine when just a handful of peas contains about 1800 milligrams of lysine. The advertising slogan that Incremin turns "extra eating into extra growth" is medically unsubstantiated and at best a half-truth. The quantities of vitamin constituents of Incremen are absurd: 10 times more vitamin B1, 25 times more vitamin B12, 2 times more vitamin B6 than required by the body daily. (1)

The daily requirement of the human body of vitamin C is about 50 milligrams, of vitamin B1 one milligram and some others in minute quantities of a few micrograms. Against these well established norms, most tonic preparations contain between 10 to 50 times the minimum requirements (2) which are simply excreted away by the body--a colossal waste of valuable nutrients in a poor country. Further, most vitamins are needed in small amounts to stimulate the processes of normal metabolism, they are not energy-giving in themselves.

It is almost certain that the high-potency multivitamin formulations consumed by the well-fed are almost wholly rejected by the body. For example, the daily requirements of vitamin C can be obtained from a single fruit or a salad helping. Vitamin A, supplied by green, leafy vegetables, is stored in large amounts by the body for proper vision. Vitamin D is naturally synthesised by the skin from daily sunlight. Despite all these simple facts, the craze for 'health' tonics continue unabated. (2).

Why ? Manohar S Kamath in his article in THE DAILY MAGAZINE provide the answers :

> "The real culprits behind the 'tonic craze' are the manufacturers of such formulations. The principal reason for their hard selling of such products that the tonics and vitamins fell in 'category four' of the Drugs Price Control Act, which means that there is no limit on profits made on these preparations. With easy pickings and a readymade market, no wonder then that every new company entering the pharmaceutical world wants to market its own brand of tonic rather than any life-saving drug;" (2)

Explaining how the 'tonic craze' is the result of systematic campaigns of the large companies, he says :

> "The first part of the plan was the mounting of an intensive sales campaign to influence doctors on the need for tonics in their day to day practice. This was followed by free sampling" (2)

"The other part of the marketing gimmickry in selling tonics was by directly advertising in the mass media, to catch the public eye. Slogans like "Do you feel tired at the end of the day? You need..." or "A woman needs iron every day" gradually made a deep impact on the people until many were psyched into believing that they could not do without a tonic."(2)

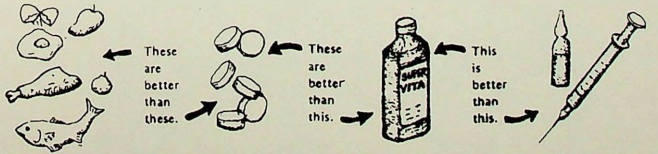
Waterbury's Yellow Label Tonic, a brand leader in the Indian tonics markets, contains only 3 milligrams of iron per teaspoon just 1/10 of which may be absorbed by the body. The Indian Council of Medical Research (ICMR) recommends at least 10 milligrams for women. The producer claims that this tonic stimulates appetites and builds bodies. But chemical analysis has revealed that it has 10% alcohol content which is the real appetite-stimulant : (1),

We have noted that these tonics are not consumed by the poor but mainly by the relatively rich whose ordinary diet adequately meets their vitamin and other requirements. In recent years, evidence has grown that the excessive vitamins may not simply be discharged by the body but may even cause severe disorders. Prolonged consumption of excessive viramin C may form kidney stones, excessive vitamin A may cause diseases of the hair, skin and liver and vitamin D in excess may cause disorders of the kindneys and bones. (2)

Take this further example from South East Asia. In the U.K., Sanatogen is marketed as a 'nerve tonic' for old women who believe in its doubtful ability to tranquilise. But Sanatogen Powder is marketed to students in Malaysia who believe in its ability to stimulate their minds. "Worried about exams?" says the advertisement. Sanatogen will give you "Greater energy and concentration". Can a drug both stimulate and sedate? (3)

A person who eats well does not need extra vitamins.

THE BEST WAY TO GET VITAMINS:



Thus, the sheer irrationality and deliberate exploitation of consumers through this sinister "tonic racket" is obvious. The fact that many such, rackets' continue unabated is a measure of the enormous influence and power of the large pharmaceutical corporations not only in India but in many other countries, particularly the developing ones.

More than 20 years ago, the following words were spoken before the Kefauver Committee hearings on drugs in the U.S.A.:

"The incidence of disease cannot be manipulated and so increased sales volume must depend atleast in part on the use of drugs unrelated to their utility or need, or in other words, improperly prescribed. Human frailty can be manipulated and exploited and this is fertile ground for any one who wishes to increase profits. The enormous sales of so-called tranquillisers are only a small part of the crop reaped from this ground. The pharmaceutical industry is unique in that it can make exploitation appear a noble purpose." (4)

Source: Aspects of the Drug Industry in India C E D.

References:

1. Health for the Millions, VHAI, April-June 1981
2. "Some Boost, and at what price?", The Daily Magazine, 7 May 1981.
3. The Impact of multinational corporations on Health in Developing Countries, by Charles Medawar, Seminar on Health, Food and Nutrition, Consumers Association of Penang, Malaysia, 15-20 Sept 1977.
4. Drugs and the Common Man, Science Today, November 1970.

The 10 Commandments of Drug Companies

1 ***Thou shalt have tens of thousands of drugs.***

2 ***Thou shalt not question the price of a drug.***

3 ***Thou shalt not tamper with nature's garden.***

4 ***Thou shalt respect thy doctor more than thyself. He knows best.***

5 ***Thou shalt betray thy people and thy nation for petty rewards.***

6 ***Thou shalt not covet, court or subscribe to any other system of medicine.***

7 ***Thou shalt not reveal company secrets.***

8 ***Thou shalt first seek remedies for "American and European" ailments.***

9 ***Thou shalt be a dumping ground for banned drugs.***

10 ***Thou shalt be a guinea pig for new and untried drugs.***

Antidotes to the Drug Industry

1 ***Let there be an essential drugs list.***

2 ***Let people know the difference between the essential and non-essential drugs.***

3 ***Let there be enough of essential drugs available and produced within the country.***

4 ***Let there be plenty of herb gardens, catalogues and clearing centres.***

5 ***Let people know how to treat their doctors.***

6 ***Let there be a link-up of conscientious doctors/ like minded people.***

7 ***Let there be a boycott of all products of the companies who violate the code of ethics.***

8 ***Let there be quick exchanges of information on marketing practices / banned products / cautions.***

9 ***Let there be counter advertisements and quick exchanges of information among journalists and educators.***

10 ***Let there be an awakening of the people to the rational use of drugs.***

Augustine J Veliath

Presented at the National Convention of CHAI on Rational Use of Drugs, Nov. 1984.

Towards a rational Drug Policy: Initiatives in the country

1 **Arogya Dakshata Mandal, Pune** has been raising awareness about drug related issues among medical professionals and the lay public since the past 8 years. They publish a monthly - 'Pune Journal of Continuing Health Education' - on drug issues and have also brought out a book 'Rational Drug Therapy' in December 1984.

They launched a movement called 'Operation Medicine' in 1977 against irrational prescription of vitamins, tonics and tinned foods.

2 **All India Drug Action Network:** A number of groups have been working in the field of drug related issues at various levels during the past 3-4 years. They have been in contact with each other and have been working informally together sharing information, putting forward a memorandum (demanding a Rational Drug Policy), participating in campaigns, lobbying with government etc. In August 1984, they felt the need to have a more organized base and have formed the All India Drug Action Network.

3 **Lok Vigyan Sanghatana, Maharashtra,** or the People's Science Movement have launched campaigns about anaemia and irrational anti-anaemia drug preparations and also about over - the - counter drugs. They organize jathas, hold district/ town seminars, write in the mass media etc.

4 **Kerala Sastra Sahitya Parishad** is a voluntary non-government organization consisting of scientists, doctors, engineers, social scientists, teachers, students, workers, peasants, technicians who are committed to popularising science and channeling it for social revolution. The KSSP has recently decided to take up the Drug issue and initiate a big campaign to expose the anti-people and exploitative tactics of the Multinational Drug Companies. The question of essential versus non-essential and dangerous drugs, the inadequacy of drug safety control measures, the rising prices of life saving drugs and the non-implementation of the Hathi Committee recommendations are the highlights of the programme.

5 **LOCOST** or Low Cost Standard Therapeutics is a collective voluntary enterprise for rational therapeutics. LOCOST aims to promote low cost, scientifically tested medicine under generic names. LOCOST is a response to a growing demand and challenge of the voluntary health sector to meet the needs of the deprived sectors of the society for not only low priced but also good quality medicine. LOCOST includes procurement, quality testing and control, distribution and educational efforts, and is located in Gujarat.

6 **Bangarapet Mission Tablet Industry** in Karnataka is a successful small scale venture providing low cost, good quality formulations to some mission hospitals in the country.

7 **Low Cost drugs and Rational Therapeutics Cell of the** Voluntary Health Association of India, New Delhi, has been instrumental in bringing together various groups in India on the issue of drugs. They have been providing informational backing to these groups, organizing meetings, informally coordinating some action etc.

8 **Medico friends circle** is a group of socially conscious individuals, interested in the health problems of our people. Through their monthly bulletin, they discuss drug issues among others. They have formed a Rational Drug Policy Cell and have launched a campaign on anti-diarrhoeals.

9 **The Kurji Holy Family Hospital Formulary** is the result of the accumulated experience of the hospital over the last 10 years. It gives a comprehensive list of drugs to treat 98% of the hospital admissions. It also gives the generic name, dosage, indications, contra-indications and side effects of these drugs. Information about comparative cost of treatment is also provided.

10 **State Forums:** During the past year drug action forums have been active in Andhra Pradesh and West Bengal. Drug Action forums are also being initiated in Gujarat and Orissa.

11 **The Pharmacology Department of the Post-Graduate Institute of Medical Education and Research, Chandigarh,** provides un-biased technical informtion on drugs and therapeutics through a monthly publication 'The Drugs Bulletin'.

12 **Others:** The following organizations have also been involved in drug related issues and are part of the All India Drug Action Network:

Consumer guidance Society of India, Bombay

Comsumer Education Research Centre, Ahmedabad

Federation of Medical Representatives Association of India

Health Services Association, Calcutta

Delhi Science Forum, New Delhi

People's Participation in Science and Technology, Madras/ Bangalore

Centre for Science and Environment, Delhi

Centre of Social Medicine and Community Health, J N University, New Delhi.

from page 14

To frustrate the move (i.e., introduction of schedule X) owners of the retail drug shops under the leadership of their powerful Association had protested by closing their shops for three days and subsequently many of them stopped storing drugs under Schedule X (even such essential drug like phenobarbitone to the great inconvenience of millions of epileptic patients!). The only plea of the shop owners being that the introduction of this schedule would increase their clerical burden as they have to maintain proper inventory. Their plea seems to lack substance in as much as legally drugshop owners are supposed to keep inventories of all items of prescription drugs coming under different other schedules. Could it be that their real difficulty lies elsewhere? It is wellknown that majority of the drugshops in our country are run without a qualified staff (i.e., a pharmacist) Only a pharmacist is eligible to record his signatures on the prescriptions while dispensing a drug under Schedule X as required by the Rule.

Courtesy:
Drug Disease Doctor
Vol. 2 No. 4/1987

What can we do?
- Support them
- Join them
- Keep them informed about what you are doing

RESOURCE MATERIALS

People, Pills and Prescriptions, column in MEDICAL SERVICE since May-June 1984.

Understanding the Drug situation in our Hospitals, a check list.

Towards a People-Oriented Drug Policy, Special Convention Issue of MEDICAL SERVICE (October-November 1984)

Prescribing Drugs

Questions to ask yourself before writing a prescription.

1. Need	Is this drug really necessary ? Is it being given to make the patient feel that something is being done ?
2. Aim	What aim is to be achieved by this drug ? What disorder of function is to be corrected ? What symptom/s have to be relieved ?
3. Knowledge	What is the approved or generic name ? What class does it belong to ? What are its characteristics ? Do I have the requisite experience or knowledge to use it ? Have I weighed the potential toxic effects against the benefit ?
4. Route and Dosage	By what route, in what dose and at what intervals is the drug to be given and why ? In what form/s does the drug come ?
5. Alternatives	Have I selected the best agent available for this particular purpose ? What other remedies might have been chosen ? How do these compare in efficacy, safety, cost ?
6. Duration	For what period of time, days, weeks or months will it be advisable to continue therapy ? When and how could a decision be made to stop ?
7. Observations	What observations can be made to judge whether the aim has been achieved ? When should they be made and by whom ? What laboratory investigation if any would help in this assessment ?
8. Elimination	How is the drug eliminated ? Will the patients illness change the usual pattern of distribution, effects or elimination of the drug ?
9. Unwanted effects	What are the side effects or toxic effects of the drug ? Are they acceptable ? How frequent are they ? How can they be modified/managed ?

10.	Precautions	Have I checked for the following : a. possible allergic risks b. possible idiosyncratic reactions c. patients drug diet which may interfere with the drug What precautions can I take to ensure continuation of therapy.
11.	Contraindications	Are there any conditions in which this drug is contraindicated ? Are these 'absolute' or 'relative' ? Are there any drugs which should be avoided when the patient takes this treatment ? Which and why ?
12.	Patients point of view	What does the patient believe about the drug ? What has he been told about it ? And what has he remembered ? Does he need additional information ?
13.	Patient reliability	Does his relative need additional information ? Is the patient reliable for this type of therapy ? Will he need/get proper supervision by relatives or attendants ?
14.	Cost	Is the drug the cheapest drug of that type ? If not could a cheaper drug do the job as well ?

15. Finally is there anything else I need to know about this drug ?

Adapted from :

i. A Herxheimer : The Lancet II 1186-1187, 27th Nov 1976

ii. Formulary and Therapeutic guide—Kurji Holy Family Hospital

iii. Prescribing drugs — MNAMS Handout, Dept of Pharmacology, St John's Medical College, Bangalore

What Can We Do ?

1. Educate ourselves	We should make an effort to avail ourselves of all the available materials on drugs. We should purchase some of the books and subscribe to some of the journals and bulletins mentioned in 'widening horizons' to keep ourselves upto date.
2. Share and Disseminate information	We should circulate all the information and resources to all our staff and to other colleagues and centres through all possible channels of communication. We could share our own initiatives and experiences.
3. Adopt essential drug list	We should draw up an essential list for our institution in which cost, efficacy, safety and quality will be important criteria (refer to WHO's suggested list) We could purchase and stock drugs in accordance with this list.
4. Adopt generic	We could use/adopt the generic drug concept during purchasing, prescribing or dispensing drugs.
5. Stop Irrational prescribing	Could stop prescribing drugs whose only advertised values are :— a. cosmetic embellishments b. elegant packing c. irrational combinations d. imitative drugs e. inadequate evidence of greater value We could weed out 'banned drugs' as well as restricted drugs. We could stop 'injection and tonic' practice.
6. Avoid Drug Industry Linkages	We could refuse to take gifs and physician samples We could avoid allowing drug companies to sponsor events/ meetings We could beware of unethical trade discounts or other forms of inducement
7. Adopt Rational : Drug Purchase	We could adopt bulk purchasing Support cooperative purchasing or production endeavours Produce drugs in your hospitals/dispensaries.

8.	Adopt open policy to non-allopathic systems and non-drug therapies	We should be open to other forms of treatment. Seek information and be willing to incorporate it in our work Share our experience with others Send our staff for training in these forms of treatment if necessary.
9.	Support networks/ organization/ consumer movements taking up drug issues.	Find out about all such groups at local, regional, state level or national level Support and participate in their activities.
10.	Promote 'Health for all' priorities.	We should actively promote the following in our work : a. simple home remedies b. herbal remedies and herbal gardens c. health education and patient awareness d. training of village level workers e. community health initiatives f. development programmes g. awareness building.

Reporting in 1956 on the excessive amount of space taken up by advertisements in Indian newspapers, the Indian Press Commission commented :

"The largest field of..... objectionable advertising which we feel should be put down by law is of drugs and proprietary medicines.....The volume of advertising of such commodities ranks next only to the volume of advertising of cosmetics.

—Use and Misuse of the Media
Sumanta Banerjee, World Health, Feb-March 1983

Consumer Alert - Consumer Action

Ravi Narayan

The Problem

The Indian Council of Medical Research (ICMR) and the Indian Council of Social Science Research (ICSSR) have, in a joint study group report entitled "Health for All — an Alternative Strategy" warned that 'eternal vigilance is required to ensure that the health care system does not get medicalised, that the doctor-drug producer axis does not exploit the people and that the abundance of drugs does not become a vested interest in ill-health'. This warning is a serious indictment of the drug industry and the medical profession in the country. It confirms the growing evidence that drugs are being pushed on an unsuspecting public by devious methods which masquerade as 'sales promotion' of drug companies and 'professional prescribing practice' by doctors.

A spate of reports have been appearing in our newspapers and periodicals of late, on drug related issues and a review of these highlight that many of the following practices are not at all uncommon in India.

(i) Sale of drugs banned in other countries eg: Lomotil and Clioquinol preparations.

(i) Sale of irrational combinations and formulations eg: Hathi Committee has suggested weeding out of atleast 23 such preparations.

(iii) Sale of drugs without adequate precautionary product information.

(iv) Sale of drugs at highly inflated costs eg: it is reported that Analgin is being sold at 20 to 30 times the cost of production.

(v) Promotion of drugs for indications that are not clinically proved and are often potentially dangerous eg: Promotion of EP forte combinations for pregnancy testing and induction of abortion. There is well documented scientific evidence that risk of foetal deformity is increased by the use of these hormonal preparations.

(vi) Sale of spurious, adulterated or poor quality drugs eg: Turmeric powder in tetracycline capsules and poor quality and reaction producing intravenous fluid preparations have been reported.

(vii) Sale of old, expired and unused drugs. There is the double danger of effects of denatured drugs as also of inadequate dosage.

(viii) Over-prescription and misuse of tonics, high protein foods, hormonal preparations and baby foods that are both superfluons and a drain on the family economy.

(ix) Production of drugs for profits rather than health needs of people eg: The ICMR/ICSSR report highlights that drugs for diseases like leprosy and tuberculosis which affect millions are produced at one third and one fourth of the actual requirements while tonics, vitamins and high protein substitutes are being produced in wasteful abundance.

(x) Sale of drugs over the counter without doctors' prescriptions or the necessary statutory checks.

It is evident then that what is needed in the country today is a consumer awakening and awareness building process that will sensitise people to the realities of the drug industry, mobilise public opinion, sensitise policy makers, confront the medical establishment and challenge the drug industry. This process will have to the initiation, promotion and sustenance of consumer action to ensure that the drug policy in India is more 'people' and 'health' oriented. Is there any evidence of such an awareness ?

Consumer alert and action

Beginning in the late seventies, there is an increasing number of organisations, associations, projects and action groups who have begun to create an awareness of drug-related policy issues. These groups are predominantly if not exclusively urban-based, consisting of young professionals and intellectuals from different ideological backgrounds.

Since the Medical Profession is the 'instrumental consumer' ie., they prescribe the drugs, many of these groups have directed their efforts particularly towards them. Many others are health or development associations, science popularising movements and consumer associations who are increasingly taking up drug-issues as one of their many activities.

The main types of action they have been involved in are :—

1. **Meetings :**

* *'The Drug Industry and the Indian People'* organized by Delhi Science Forum, Society of Young Scientists, Federation of Medical Representatives Association of India (FMRAI) and others in Delhi, November 1981.
* *'Drug Issues and Feasible Alternatives'* by Voluntary Health Association of India (VHAI) at Pune, January 1982.
* *'Drug use and Abuse'* by medico friend circle (mfc) of Tara, June 1982.
* At the *All India Convention of People's Science Movements* at Trivandrum, organised by Kerala Sastra Sahitya Parishad (KSSP). A health group was formed to coordinate joint action programme specially on drug issues.
* Seminar on *'National Health Policy'* by VHAI, Concern for Correct Medicine (CCM), All India Women's Conference (AIWC) and others in Delhi, April 1983. Drug issues were also discussed.
* Meetings on *'Drug Policy Issues'* were held in Pune, Bombay, Trivandrum, Madras, Bangalore and Delhi during Dr Zafarullah Chowdhury's (of Gono-shasthaya Kendra) whirlwind tour of India in November-December 1983. These 'galvanised everyone into more action'. National and local press gave coverage right along the tour.
* FMRAI Annual Convention in New Delhi, December 1983 made a 27 point charter of demands which included demands for *Rational Drug Policies* relevant to the health needs of the country effective drug control, ban on irrational and hazardous drugs.
* *Misuse of Drugs* — Seminar organised by the Andhra Pradesh Voluntary Health Association at Hyderabad in February 1984.
* *'Drugs vs. People'* — A Seminar organised by West Bengal Voluntary Health Association at Max Muller Bhavan at Calcutta in February 1984.
* *'Low Cost — Cost effective health Care'*, one day symposium organised by Kerala Voluntary Health Services.

2. **Educational Campaigns**

* Arogya Dakshata Mandal (ADM) Pune, launched a movement called *'Operation Medicine'* in July 1977 against irrational prescription of vitamins, tonics, and tinned foods.

* VHAI along with many associates launched a campaign in March 1982 (International Women's Day) against the misuse of hormonal preparations for pregnancy testing.

* National Alliance for Nutrition of Infants (NANI) was formed to promote breast feeding and prevent control of promotion of commercial milk foods and substitutes.

* mfc launched campaign for rational management of diarrhoea with ORT, and prevent misuse abuse of available anti-diarrhoeals.

* Lok Vidnyan Sanghatana, Maharashtra (PSM) launched a campaign about anemia in women and irrational anti-anaemia drug preparations is the market, in May 1983.

* FMRAI have launched a separate campaign against irrational practices and role of multinational corporations in pharmaceutical industry in India.

* KSSP has organised jathas (Science and Cultural Marches) through the villages and towns of Kerala in October-November 1983 on *'War : the war against unscientific practices in the field of drug industry.*

* Drug Action Network launched a nation wide signature campaign in April 1984 to demand for a Rational Drug Policy. This campaign involves activist and consumer groups civil liberties grievances, health professional associations.

* KSSP launched a campaign for a 'People's Drug Policy' on April 7th World Health Day. District level Seminars were held in all the 13 districts of the State. On October 2nd, the Sastra Kala Jatha was launched with signature campaign. Slide shows, art forms etc. Two seminars—"The Indian Drug Industry' and the People's Needs" and 'A Drug Policy for Kerala' are planned for November 1984.

3. **Publications**

* mfc published two anthologies — 'In Search of Diagnosis' (1977) and 'Health Care Which Way to Go' (1982) which included many articles on drug issues.

* VHAI published special issue of their bimonthly—Health for the Millions—in 1981. Thematic issue was entitled 'Medicine as if people mattered'.

* Centre for Education and Documentation (CED), Bombay, published an exhaustive well researched book called 'Aspects of Drug Industry in India'.

* Indian Social Institute (ISI) New Delhi, brought out an Indian edition of the book 'Insult or Injury' by Charles Medawar of Social Audit (UK) which is a study of practices of British Pharmaceuticals and Food Industry in Asia.

* 'Taste of Tears' is a recent publication of VHAI on problems of diarrhoea and its management.

* Consumer Education and Research Centre, Ahmedabad, prepared a well documented report on Analgesics and submitted it to the Drugs Controller.

This report deals with hazardous and irrational combinations.

* Rational Drug Therapy — first volume of the book by Arogya Dakshak Mandal, expected in December 1984.

4. **Bulletins/Journals**

* Pune Journal of Continuing Health Education, by Arogya Dakshata Mandal, sensitises its readers to the half truths of medical advertising apart from providing reliable scientific information.

* 'Drugs Bulletin' — of Pharmacology Department of Post-Graduate Institute, Chardigarh is a authentic and authoritative resource on drugs in India.

* Handouts of the Low Cost Drugs and Rational Therapeutic Cell of VHAI have covered an extensive range of drug prescribing and policy issues.

5. **Low cost Drugs venturs**

* Bangarapet Medical Mission Tablet industry is a successful small scale venture providing low cost, good quality formulation to a limited group of mission hospitals in the country.

* LOCOST a collective voluntary endeavour in Gujarat for rational therapeutics through the promotion of low cost, quality generic medicines. It also plans an educational effort for minimum use of drugs and increased awareness of the socio-economic implications of irrational therapeutics.

6. **Public Interest Litigation**

* Vincent Panikulangara, a lawyer from Kerala, filed a writ petition in the Supreme Court, regarding the ban of the import, manufacture, sale and distribution of drugs identified as hazardous and or irrational by the Drugs Consultative Committee of the Government of India. This was done on behalf of the people of India.

7. **Networking**

* All these groups have now come together to form the All India Drug Action Network. Regional and State level network are also forming up, eg : West Bengal Drug Action Forum, Hyderabad Drug Action Forum. DAN also bring out the Drug Action Network Newsletter which keeps the network up-to-date on activities and ideas of all the groups. DAN meets twice a year to plan and coordinate its activities.

Towards a People's Movement

All the above efforts are small steps towards a much more wide based consumer movement against drug use and abuse and profit oriented drug policies. However, it must be remembered that in a country like ours when a very large percentage of people are below the poverty line and when more than 75 percent of the people have little access to basic health science a consumer action programme only on drug matters will continue to be cut off from the needs and aspirations of the majority.

Dr Norman Bethune, Famous for his work in China, wrote *'The best form of providing health care and health protection would be to change the economic system whica produces ill health-to liquidate ignorance, poverty and unemployment'*.

One hopes that eventually drug related issues will become part of a much wider people's campaign for health, development and socio-political change because at the root of the entire problem of drug production and availability lies what Ivan Illich has aptly described as 'Social-iatrogenesis-ie., health policies reinforcing an industrial organisation which generates ill-health'.

Source : Bulletin of Science December 83 Jan. 84 (up dated

Drug Utilisation Survey Report

This survey was conducted by the National Institute of Nutrition (NIN) in cooperation with the Directorate of Drug Control Administration and AP Chemists and Druggists Association, Hyderabad in the twin cities of Hyderabad and Secunderabad covering 10% of the 330 retail pharmaceutical shops.

Some of the findings of the survey are as follows:

- self medication rate was an alarming 46%.
- 27% of the doctors' prescriptions were for 3 to 4 drugs Only 4.3% of prescriptions were for more than 4 drugs.
- the maximum number of prescriptions were for Nutritional Products (tonics, enzymatic preparations and vitamins), then antiinfectives (antibiotics and sulfas) and then analgesics.
- 58% of the self medicated drugs were schedule 'L' and 'H' drugs which cannot be sold without prescription, nor should be consumed without medical supervision, because of the associated major side effects and toxicity.
- amongst self administered drugs analgesics, nutritional products and antibiotics topped the list.

Analgesics, antipyretics and anti-inflammatory drugs:

- 30.2% of the self prescribed analgesics, antipyretics and anti-inflammatory agents were scheduled drugs. These were mainly analgin, phenylbutazone (with or without corticosteroids) and ibuprofen.
- an earlier survey by the CERF (Consumer Education and Research Centre, Ahmedabad) had shown that of 13 over-the-counter brands of these drugs, 11 did not provide any information. The 44 doctors interviewed reported seeing on an average 8 to 10 cases of drug

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drug poisoning per month.

Vitamins and Tonics:

- only 31% persons surveyed had a correct concept regarding nutritional supplements. The majority held the erroneous view that daily consumption of tonics was essential for health. The credit for this false belief goes to advertising pressure as well as doctors' prescription practices.

- 16% of the doctors had prescribed simultaneously more than one vitamin preparation having the same ingredientsin various dosage forms.

- iron deficiency anemia, B2 deficiency, were the commonest deficiencies in the population but sales of B Complex (B1, B2, B6 B12) combinations and other vitamins topped the list of sales figures.

Antibiotics:

- over 30% of the doctors' prescriptions contained antibiotics.
- approximately 12.8% of self-prescribed drugs were antibiotics.
- most antibiotic prescriptions were for sulfa and trimethoprim combinations, tetracyclines and penicillin, in that order.
- tetracycline, sulfa-trimethoprim and penicillin were the most popular self-prescribed drugs.
- 30% of the antibiotics purchased for self medication were for less than a day. Only 18% were purchased for a full course of five days. Only 40% of prescriptions for antibiotics were bought for five days.

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The findings of the NIN and CERC surveys indicate the urgent need for public education where disease and drugs are concerned.

Source: The Drug Action network: Newsletter of the Low Cost Drugs and Rational Therapeutics Cell, VHAI, New Delhi.

Minutes of the Third Meeting of the Drug Action Forum Karnataka held on 4th December 1988.

The Drug Action Forum-Karnataka met on the 4th December 1988 at the office of the People's Trust at 10.30 AM. The meeting was attended by the following members :

1. Mr N C Nanaiah
2. Dr Satish Kumar
3. Mr R B Hiremath
4. Dr Vanaja Ramprasad
5. Mr K Gopinathan
6. Dr Gopal Dabade.

The agenda taken up for discussions were :-

(1) Objectives of the Forum.

(2) Structure/Members of the Forum.

(3) Dissemination of information.

(4) Mobilisation of funds.

PROCEEDINGS

1. Objectives of the Forum
(At the second meeting held on 6th November 1988, it was decided to register the DAF-K as a Society and the Co-ordinator has been given the necessary consent to go ahead with the preliminary work of registration.)

The members discussed this item in great detail and suggested the following as the likely objectives of the Society :

1. To build awareness amongst general public with regard to the usefulness/uselessness/benefit-risk ratio of various systems of medicine in practice.
2. To undertake studies both in rural and urban areas to focus on issues around rational use of drugs, use of banned drugs, economics of prescribing generic Vs brand names and other similar studies which would help the government authorities in formulating a people oriented drug policy.
3. To disseminate information on the findings of the study and other related matters through newspapers, educative magazines, journals, exhibitions, films, slides and TV coverage.

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4. To dialogue with physicians through the IMA and similar bodies on rational drug therapy.
5. To conduct training programmes, workshops and seminars on matters related to drug issues.
6. To interact with the voluntary organisations involved in health and development in Karnataka in regard to the importance of practice of rational drug therapy.
7. To co-ordinate and collaborate with national and international bodies working in a similar direction.
8. To function as a pressure lobby and initiate steps for enforcement of ban of any drug.
9. To bring out a Newsletter in course of time.
10. To initiate centres of Drug Action at district level and co-ordinate with them.

2. The structure/members of the Forum

A decentralised structure with an apex body located in Bangalore was thought appropriate. To initiate the district based network of the forum it was suggested that voluntary organisations based in different parts of Karnataka and preferably with doctors involved in these programmes have to be identified and these individual centres work independently and in union with the apex body. In order to promote this idea and co-opt members into the apex body, it was proposed that discussions have to be held individually and collectively with the following members and to invite their suggestions and reactions on the above aspects.

1. Dr C M Francis
2. Mr Premanand Shetty - Ex-Drug Controller, Karnataka
3. Mr Shanbaug - Ex-Drug Controller, Karnataka
4. Dr Mira Shiva
5. Mr Jagadeesh Mundaragi
6. Dr Ravi Narayan
7. Dr H Sudhershan
8. Dr Gerry Pais
9. Dr S B Maheshwara
10. Dr Anand Kabbur
11. Dr Shyama Narang
12. Mr N B Joshi
13. Dr Dhruv Mankad
14. Mr B V Sesha

and those who were present at the meeting.

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The address for the registered office is still being considered.

3. Dissemination of information

Dissemination of information to the public was given enough thought during the meeting. Having an independent bulletin either in English or in Kannada or in both though may be necessary in the long run, it was considered more economical to use other bulletins or journals that are already existing to disseminate information. The use of the T.V. through the Bangalore Doordarshan was contemplated and it would be explored by Dr Satish Kumar and Mr Nanaiah.

4. Mobilisation of funds

To begin with, the Forum will not depend on any assured source of funds for the conducting of the LAF-K activities. It was suggested by the members that the Forum approach various agencies in India including Karnataka Rajya Vignana Parishad as also appeal to individuals for donations, for specific projects.

5. The next meeting

The next meeting was fixed for the 4th of January 1989 at the office of the People's Trust at 2 PM.

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3. Mr R B Hiremath
4. Dr Vanaja Ramprasad
5. Mr K Gopinathan
6. Dr Gopal Dabade.

The agenda taken up for discussions were :-

(1) Objectives of the Forum.

(2) Structure/Members of the Forum.

(3) Dissemination of information.

(4) Mobilisation of funds.

PROCEEDINGS

1. Objectives of the Forum
(At the second meeting held on 6th November 1988, it was decided to register the DAF-K as a Society and the Co-ordinator has been given the necessary consent to go ahead with the preliminary work of registration.)

The members discussed this item in great detail and suggested the following as the likely objectives of the Society :

1. To build awareness amongst general public with regard to the usefulness/uselessness/benefit-risk ratio of various systems of medicine in practice.
2. To undertake studies both in rural and urban areas to focus on issues around rational use of drugs, use of banned drugs, economics of prescribing generic Vs brand names and other similar studies which would help the government authorities in formulating a people oriented drug policy.
3. To disseminate information on the findings of the study and other related matters through newspapers, educative magazines, journals, exhibitions, films, slides and TV coverage.

.....2

The address for the registered office is still being considered.

3. Dissemination of information

Dissemination of information to the public was given enough thought during the meeting. Having an independent bulletin either in English or in Kannada or in both though may be necessary in the long run, it was considered more economical to use other bulletins or journals that are already existing to disseminate information. The use of the T.V. through the Bangalore Doordarshan was contemplated and it would be explored by Dr Satish Kumar and Mr Nanaiah.

4. Mobilisation of funds

To begin with, the Forum will not depend on any assured source of funds for the conducting of the LAF-K activities. It was suggested by the members that the Forum approach various agencies in India including Karnataka Rajya Vignana Parishad as also appeal to individuals for donations, for specific projects.

5. The next meeting

The next meeting was fixed for the 4th of January 1989 at the office of the People's Trust at 2 PM.

.....

Minutes of the Third Meeting of the Drug Action Forum Karnataka held on 4th December 1988.

The Drug Action Forum-Karnataka met on the 4th December 1988 at the office of the People's Trust at 10.30 AM. The meeting was attended by the following members :

1. Mr N C Nanaiah
2. Dr Satish Kumar
3. Mr R B Hiremath
4. Dr Vanaja Ramprasad
5. Mr K Gopinathan
6. Dr Gopal Dabade.

The agenda taken up for discussions were :-

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.....2

4. To dialogue with physicians through the IMA and similar bodies on rational drug therapy.

5. To conduct training programmes, workshops and seminars on matters related to drug issues.

6. To interact with the voluntary organisations involved in health and development in Karnataka in regard to the importance of practice of rational drug therapy.

7. To co-ordinate and collaborate with national and international bodies working in a similar direction.

8. To function as a pressure lobby and initiate steps for enforcement of ban of any drug.

9. To bring out a Newsletter in course of time.

10. To initiate centres of Drug Action at district level and co-ordinate with them.

2. The structure/members of the Forum

A decentralised structure with an apex body located in Bangalore was thought appropriate. To initiate the district based network of the forum it was suggested that voluntary organisations based in different parts of Karnataka and preferably with doctors involved in these programmes have to be identified and these individual centres work independently and in union with the apex body. In order to promote this idea and co-opt members into the apex body, it was proposed that discussions have to be held individually and collectively with the following members and to invite their suggestions and reactions on the above aspects.

1. Dr C M Francis
2. Mr Premanand Shetty - Ex-Drug Controller, Karnataka
3. Mr Shanbaug - Ex-Drug Controller, Karnataka
4. Dr Mira Shiva
5. Mr Jagadeesh Mundaragi
6. Dr Ravi Narayan
7. Dr H Sudharshan
8. Dr Gerry Pais
9. Dr S B Maheshwara
10. Dr Anand Kabbur
11. Dr Shyama Narang
12. Mr N B Joshi
13. Dr Dhruv Mankad
14. Mr B V Sesha

and those who were present at the meeting.

.....3

The address for the registered office is still being considered.

3. Dissemination of information

Dissemination of information to the public was given enough thought during the meeting. Having an independent bulletin either in English or in Kannada or in both though may be necessary in the long run, it was considered more economical to use other bulletins or journals that are already existing to disseminate information. The use of the T.V. through the Bangalore Doordarshan was contemplated and it would be explored by Dr Satish Kumar and Mr Nanaiah.

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5. The next meeting

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.....

minutes of the fourth dialogue with the network group held on 05.12.1988 at ashirvad.

Members present

1. Gopal Dabade (GD)
2. Joseph Panackel (JP)
3. Gerry Pais (GP)
4. KV Sridharan (KVS)
5. H Sudarshan (HS)
6. BS Paresh Kumar (BSPK)
7. Maria Zillioli (MZ)
8. Uma Sridharan (US)
9. Vanaja Ramprasad (VR)
10. V Benjamin (VB)
11. Sujatha D'Magrey (SDM)
12. G Gururaj (GG)
13. S P Tekur (SPT)
14. K Gopinathan (KG)
15. Ajith Lalwani (a medical student from UK)

KG welcomed the members and briefed the new members the idea of getting together of various individuals involved in health and development work, in such a platform, where the views and experiences of each of them could be shared for the benefit of one another. He then requested the members especially those who have started new experiments to share their experiences.

GD He had started his community health programme in a place called KULAVALLI (cluster of 7 villages) in Kittur, 30 kms away from Dharward. This is an area, where the Government has entered into an agreement with Messrs Karnataka Pulpwood Limited for eucalyptus plantation. In his experience it was found that eucalyptus cultivation was not at all an issue for the villagers. Their need was for land, school, power supply and so on. The villages are not accessible by motor transport. People use cycle, bullock cart etc. The village belonged to one Inamdar (area being 1700 acres). The land was a gift to Inamdar by British, for helping them catch one Sangoli Rayanna. This land is occupied by poor people without obtaining the legal rights. There is a nationalised bank, the services of which are not utilized by the villagers; they consider the bank employees "Englishmen". The villagers, however, frequent a bank called "Boot Bank", who charges 250% interest. The bank got this peculiar name because the defaulters are dealt with their 'boots'.

The total population of these villages is 2777. Forest dwelling is the main occupation. Two community health guides attached to Kittur PHC visit these villages. General Practitioners visit these villages, spending an hour a day in each village. Muslims and Nayakas are the communities.

.....2

GD's modus operandi is to stay overnight in these villages and meet the people discussing with them to find out their felt needs. One of their felt needs was education and they wanted a school and they agreed to contribute whatever they have (like bricks, wood, leaves etc.) to build a shed. But the question was what sort of education they should give. Anyway the school started functioning on a non-formal basis, in the evenings. It was decided that no health programme would be initiated till the villagers asks for it.

JP: He explained about his involvement with a research study on "Community Participation in Mental Health Care" being undertaken by his department at NIMHANS. The area covered is under Jugani with a 75000 population, where the people contribute to a Health Fund. Although the study is titled as "Participation", there exists only "quasi participation", due to ICMR wanting their "conventional project protocol". JP started interviewing the people to know what they are wanting in the health field and to identify their priorities. The method of getting these information was by recording the discussion using a tape recorder (without the knowledge of the interviewee.)

KVS/US: During the past few months they were visiting various projects in Andhra Pradesh, Tamilnadu and Orissa in connection with training/evaluation. They were recently at the Association for Sarva Seva Farms, an off shoot of Vinobhaji's Bhoodan at Madurai. KVS spent sometime at Deena Sewa Sangha, looking through the files and brought out a book called "Continuing Story of the Social Workers Brotherhood". Uma had been involved in conducting Workshops on "Communication and Education" for various projects including Anganwadi Workers under the ICDS programme. Changes needed in the educational materials and evolving new methods in communication are looked into.

GP: He now wishes to get back to health/medical field after years of involving in non-medical work. Presently he is in search of an institution where he could get an attachment to work in this area. A Consumer Service Society has been started at Hunsur where issues related to drug use/ abuse are also dealt with. On the request of some of the members, he shared his African experience to the group.

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HS: He is involved in documenting tribal knowledge on different species of trees in the surrounding areas of BR Hills including their knowledge on astronomy. A vocational training centre with a view to imparting employment oriented trade/skills on social forestry, sericulture etc., is planned.

MZ: She is involved with the School Health programme of Deena Sewa Sangh, Bangalore. Behavioural Sciences/ holistic health, children needing attention are covered in this programme with the help of Dr Malavyka Kapoor of NIMHANS. Has attended Workshops, meetings on various issues in the recent past. She is now in the process of collecting materials on development of human beings.

SDM: She briefed the group about her training programmes in Health and Development. Two 10 weeks training programmes per year are conducted--6 weeks class room teaching and 4 weeks at the field. After the training follow up visits and Workshops/participatory evaluation are conducted in the field. Topics include: health and community development; drug action; indigenous medicine; nutrition; legal aid; cooperation; leprosy; teaching methodologies; cost analysis; accounts. Every 18 months a Core Group Workshop is conducted. The participants in this Workshop being the best trainees in the preceeding training programmes. The course fee is subsidised.

VB: He is involved with a Leprosy Project at Karigiri. While interacting with the members, he gave an account of how the government can topple the initiatives of volags as also how they can influence the same volags. He told the group, an incident which took place in Tamilnadu involving an activist group (he did not want to divulge the name of the group). The activists were working with a group of women, building awareness. One one occasion this group of women marched to the Primary Health Centre and gheravoed the staff for their inaction; they also went to the DHO asking him to look into the issue in question. The situation improved. Having gained confidence, when there was draught in the area, they approached the Sub Collector demanding arrangements for water supply.

.....4

The Sub Collector ordered for immediate remedial action. The Government at Madras were surprised to learn of the effectiveness of the Women's group and asked the authorities to conduct an enquiry into the happenings to find out who was behind the group. Under "law and order" problem, the activists records were confiscated and the staff except the Director (who was not in station) were taken to police custody. After the incident, the staff arrested by the polic left the organization and the Director continues his work in accordance with the wishes of the government officials, with government assistance.

VB also mentioned about a funding agency who refused to continue supporting a project on the ground that "the work of the project was in line with the government policies".

There was some discussion on the following broader issues arising out of points mentioned by those of the participants who shared about their work:

1. Government initiatives often overlook the interests and needs of the people.

2. The general masses have recognised the importance of education/literacy.

3. The conventional approach to various studies being followed by the government establishments does not allow the researchers the necessary freedom to evolve their own methodology. Actual participation of the community in the governmental programmes and or its research activities, therefore, remains only in paper.

4. New methods are to be evolved in communicating health messages to the people. Changes are to be made in the educational materials, presently available, for their effectiveness.

5. The voluntary organizations may sometime have to succumb to political pressures in order to avoid the authorities branding them as anti-government.

6. Some funding agencies do not support NGOs collaborating/ supplementing government programmes.

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SUPREME COURT OF INDIA
RECORD OF PROCEEDINGS

WP(C)No.698/93

DRUG ACTION FORUM AND ORS Petitioner (s)

VERSUS

UNION OF INDIA AND ORS Respondent

(With Appln(s). for impleading party and intervention and impleading party)
With

W.P(Civil)No.422/95

Date : 24/02/97 These Petitions were called on for hearing today.

CORAM :
HON'BLE MR. JUSTICE J.S. VERMA
HON'BLE MR. JUSTICE B.M. KIRPAL

For appearing parties : Mr. Anil B. Diwan, Sr. Adv. with Mr. Shaukat Merchant, Ms. Bina Gupta, Mr. Ramesh Singh and Ms. Rakhi Ray, Advs.

: Mr. VR Reddy, ASG.
Mr. S. Wasim Qadri, Adv. with Mr. A.D.N. Rao and Ms. Anil Katiyar, Advs.
Mrs. Sushma Suri, Adv.

Mr. KK Laroia, Adv. and Mr. Prashant Bhushan, Advs.

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Mr. Mukul Mudgal, Adv.

Ms. Vimla Sinha and Mr. Gopal Singh, Advs.

M/s. MJ Paul,
Jana Kalyan Das, DS Mehra, S.K. Verma,

After hearing learned counsel the Court made the following

O R D E R

The learned Additional Solicitor General informs us that the Core Group has indicated that the period of three months would be adequate for completion of the task by them as required by the earlier order dated 12th February, 1997. Accordingly, we request the Core Group to complete the task as expeditiously as possible and latest by the end of 31st May, 1997. The learned Additional Solicitor General will give this intimation to the Core Group through its Convenor.

We are also informed by learned counsel that the particulars of the existing stock of the drugs manufactured prior to 17th December, 1996 as required by the earlier order dated 12th February, 1997 have been furnished by the manufacturers and the same is in the process of certification by the competent authorities. The learned Additional Solicitor General also states on instructions that there is no objection by the concerned authorities to the export of fixed dose combinations of Analgin known by the brand names - Baralgan (Baralgin), Spasgan and Trigan Injection & Trigan E Tablets - which have been manufactured by some of the companies prior to 17th December, 1996 to some foreign countries wherein consumption of the same is not banned of the quantity duly certified by the competent authorities; and that the Central Government through its agencies will monitor strict compliance of the same ensuring that no part of such stock of these banned drugs would be utilised for internal consumption within the country. In view of this statement of the learned Additional Solicitor General, we allow those manufacturers to

authorities to allow them to export the certified stock of such drugs manufactured prior to 17th December, 1996 to the foreign countries wherein consumption of the same is not banned in accordance with the Government's Export Policy. The Central Government would be responsible for ensuring that the certified stock of these drugs is utilized only in this matter.

List on 14th April, 1997.

(D.P. Walia)
Court Master

(S.L. Goyal)
Court Master

14th April - Court declared Holiday ~~since~~
- Dr. Ambedkar Jayanti

...Kalyan Das, DS Mr. S.K. Verma,

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Kalyan Dass, DS Mr. S.K. Verma,

DR-13

Aspirin May Cause More Harm Than Good

Taking low dose aspirin as a preventive measure against coronary heart disease, which is a very common practice, may actually cause more harm than good, according to a just published study.

British researchers identified over 5,000 UK men, aged between 45 and 69 years, who were at increased risk of coronary heart disease but had not previously had heart trouble. The men were randomly divided into four different treatment groups to accurately establish the effect of aspirin.

The authors found a greater beneficial effect of aspirin in men with low rather than high blood pressures, not only for coronary heart disease but also for stroke, although the modest benefit does not necessarily outweigh the risk of bleeding. Men with higher pressures may derive no protective benefit from aspirin but will risk possible serious bleeding.

Given the widespread use of aspirin for the prevention of coronary heart disease, the study's authors suggest that these findings have important implications, although they admit that further trials are needed to confirm the results.

Because of the strong correlation between blood pressure found in this study, the authors also stress the importance of adequately controlling blood pressure for those in whom the preventive use of aspirin is being considered. In addition, men who have previously had heart trouble and strokes and are taking aspirin should continue to do so, unless instructed otherwise, since they are more likely to obtain a greater benefit than the general population.

British Medical Journal June 25, 2000; 321: 13-17.

COMMENT: Well, low dose aspirin for the prevention of heart disease is something that I have been wavering on for the last few years. I felt that if one

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wavering on for the last few years. I felt that if one used one-fifth of an aspirin three times a week, one could receive most of the benefits and avoid the side effects. However, it appears that, as for most every area of chronic illness, drugs are not the solution. I am changing my previously held position on this subject (see below) and advising one stop using aspirin to lower the risk of heart disease and stroke. There are far more effective therapies to do that. The **diet** is the most foundational, but exercise and certain supplements would make far more sense for most people than using a drug, even at low doses.

Related Articles:

Few Heart Risk Patients Taking Aspirin

Long Term Aspirin Use Leads To Cataracts

Aspirin, Ace Inhibitor Combination May Be Dangerous

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The following model list of essential drugs is taken from the WHO Technical Report series 770 (WHO, Geneva, 1988 "The use of Essential Drugs").

MODEL LIST OF ESSENTIAL DRUGS
EXPLANATORY NOTES

Since the first report on the selection of essential drugs was published in 1977, the concept of essential drugs has become widely applied. It has provided a rational basis not only for drug procurement at national level but also for establishing drug requirements at various levels within the health care system.

The international nonproprietary (generic) names for drugs or pharmaceutical substances should be used whenever available, and prescribers should be provided with a cross-index of nonproprietary and proprietary names.

The concept of essential drugs has been endorsed unanimously by the World Health Assembly. It is intended to be flexible and adaptable to many different situations; exactly what is regarded as essential remains a national responsibility.

The wide applicability of the concept is now evident from experience gained in many countries. Most national lists of essential drugs are stratified to reflect requirements at different levels within the health care infrastructure. Typically, a very short list has been compiled for community health workers while the most comprehensive lists have been reserved for large urban and regional hospitals.

One hundred and nine countries have now developed lists of essential drugs and more than 40 countries are making great efforts to implement programmes based on the essential-drugs concept. The priorities and approaches differ from country to country in accordance with each country's socioeconomic situation, but the conceptual basis is the same. The WHO Action Programme on Essential Drugs provides a platform for a harmonized and collective search for suitable and feasible solutions to the problem of the unavailability of the most essential drugs to the majority of the world's population.

Many drugs included in the list are preceded by a square symbol (#) to indicate that they represent an example of a therapeutic group and that various drugs could serve as alternatives. It is imperative that this be understood when drugs are selected at national level, since choice is then influenced by the comparative cost and availability of equivalent products. Examples of acceptable substitutions include :

(#) Codeine : Other drugs for the symptomatic treatment of diarrhoea such as diphenoxylate or loperamide or, when indicated for cough relief, noscapine or dextromethorphan.

(#) Hydrochlorothiazide : Any other thiazide-type diuretic currently in broad clinical use.

(#) Hydralazine : Any other peripheral vasodilator having an antihypertensive effect.

(#) Senna : Any mild stimulant laxative (Either synthetic or of plant origin)

(#) Sulfadimidine : Any other short-acting, systematically active sulfonamide unlikely to cause crystalluria.

DR-13

Hazardous, Bannable and Dumped Drugs

The issue of dumped drugs has been in the news for the past few years. The drug companies involved in the manufacture and sales of such drugs have received their due share of condemnation. Foreign governments policies, which provided scope for exports of such hazardous products have been also condemned, e.g., the Clayton Amendment Act and the U.S. Regulation.

It is well known that sales of medical technologies and drugs is a commerical enterprise, the motivation being profit rather than "service" or "welfare work".

Realising all this, the question arises as to how much can we, as citizens of India, expect our drug control authorities to safeguard our interests. The pressure from the drug industry is immense. In spite of knowing this, our expectations from the drug control authorities is high. After all our pharmaceutical industry is the most developed in the Third World. According to UNIDO, it belongs to Category V -- developed enough to be self-sufficient.

We have demanded that our imports, production and sales should give priority to essential, life-saving drugs over irrational and hazardous drugs, as per WHO's guidelines for Essential Drugs. The drug industry and its supporters allege that the concept of essential drugs is only for struggling, less developed countries of the Third World and not for a country like India, with its well-developed industry and its high and advanced level of medical expertise. However, this same lobby puts India in the category of less developed countries when it comes to the issue of banning drugs and drug control. The lobby claims that consideration of hazards over efficacy is a luxury which we cannot afford.

However, consumers anywhere in the world have the right to expect that irrational and hazardous drugs are not issued licences and that licences of banned drugs should be withdrawn as soon as possible, the ban implemented, and that all drugs in the market are quality - controlled. We have 20 per cent substandard drugs . One out of every five drugs will not be effective. With the incereasing number of spurious drugs floating in the market, the problem is beginning to take on dangerous proportions.

Since 1980 we've been concerned about this issue of dumped and hazardous drugs.

SOME BANNABLE DRUGS -- WHAT IS THE POSITION NOW

> Under Section 23 P of the Drugs and Cosmetic Act of 1940, the Central government has the power to issue such directions to the State Governments as required to execute the Drug Act. under Section 18 of the Act the State Government has the power to prohibit manufacture, distribution and sale of drugs by a gazette notification.

The sub-committee of the Drugs Consultative Committee, in its 1980 report, recommended the banning of 23 combinations of drugs, giving their reasons for such banning, 16 categories of these drugs were recommended for immediate weeding and seven of the categories were to be weeded out over a specified time. Over 500 brand drugs would be thus affected. This report was presented to the Durg Consultative Committee at a special meeting on 10.10.81, and later to the Drug Technical Advisory Board (DTAB) and the Ministry of Health and Family Welfare accepted it in 1981.

The DTAB, a Statuatory Body under Section 5 of the Drugs and Cosmetics Act of 1940 recommended banning of 18 fixed dose combinations. These drugs were randomly selected from the Pharmaceutical Guide. Out of the 350 brand names affected, 44 were marketed by the foreign sector, 8 by public sector, and 298 by private sector. Most of these drugs were being produced by national companies According to the authorities, "the purpose was to give time limit to firms who may already have purchased the bulk drugs form manufacturing the formulatios". What compassion and consideration for the drug companies!

SOME BATTLES

Halogenated Hydroxyquinoline

Ban of fixed dose combinations of halogenated hydroxyquinoline

was to be effective from 1.11.82. The date of the ban was extended to 31.3.83 through DO No. X19013/8/81-D dated 13.8.82.

High Doses of EP Drugs

Through another DO. No. 12-48/79 DC dated 26.6.82, the Drug Controller of India directed the State Drug Controllers to ban the manufacture of high dose Estrogen-Progesterone combinations from 31.3.83 and their sales from 30.6.83.

M/s. Unichem Labs, Bombay (OP 2927/82 of writ petion 2928/-82), M/s. Nicholas Labs, Bombay and M/s. Organon (now known as Infac (India) Ltd., Calcutta filed writ petitions in Bombay and Calcutta high courts challenging the ban. Their contention was that the Central Government has no powers to ban the drugs. The High Court of Bombay and the High Court of Calcutta have granted stay orders against the ban. Now these products are available in the market.

Section 10A and 26A of the amended Drugs and Cosmetics Act (April 1982) empower the Central Government to prohibit import, manufacture and sale of any drugs considered harmful/ toxic or irrational, etc. Since the matter was in court during the gazette notification of 23.7.83, this combination of drugs has not been included in it.

What is absolutely objectionable is the fact that -- inspite of the act of the Drug Controller of India's ban of the production and sale of EP drugs, M/s. Organon have managed to obtain extension of licences to manufacture these products for another two years.

Paediatric Tetracycline

Although this drug is banned in its oral liquid from to discontinue its being prescribed for children because of its often serious side-effects, it is being manufactured today as a tablet of 30mg. for children -- an example of how a company can follow the letter of law and yet disobey it without any legal consequences.

Aspirin and Vitamin C

In October 1982, M/s. Nicholas Labs, Bombay filed a writ petition in the Bombay High Court against the decision to ban the fixed dose combinations of Aspirin with Vitamin C. The Court ruled that the State Drug Controller has no power under Section 18 of the Drugs and Cosmetics Act to stop the manufacture and sales of this product. However, it would be open to the respondents as and when the law has been enacted, to pass any fesh order as it is considered necessary in accordance with the law after following procedures prescribed by the Government.

Subsequent to the Drug Amendment Act of 1.2.83, the manufacturers have again gone to court challenging the Central government and Sections 26 A and 10A on the grounds of "lack of objective criterion for such ban".

This has resulted in the FDA -- Maharashtra (which is supposed to be having the best drug control mechanism in India) informing the Drug Controller of India that, in the light of the ruling given by the Bombay High Court, "it would not be possible for him to take any action to stop the manufacture and sale of any of the fixed dose combinations in question". (Letter dated 9.6.1984 by the Drug Controller of India to the Voluntary Health Association of India).

Gazette Ambiguities

It is not clear from the DO letter banning 22 drugs, whether some drugs like strychnine and yohimbine, and caffeine are banned only in some combinations, or in all combinations :

- any drug containing yohimbine, or strychinine would be banned (as neither of the two were considered to have any therapeutic value and infact could lead to serious side effects).

- or the ban was applicable to drugs containing both yohimbine and strychnine.

- or to yomhimbine and strychnine with testesterone or vitamins

- or ONLY to drugs which contained all four : yohimbine, strychine, testesterone and vitamins.

Bangladesh banned 1742 drugs in June 1982. The time period given to the drug companies to **withdraw these products from the market, to destroy these products** was three to nine months, depending on the product. **They were strictly prohibited from exporting these products to other countries.** But we failed to ban even a few hundreds, let alone 1742 drugs. The time period given to drug companies was to complete the manufacture of their formulation and sell off their stocks.

WHO IS MORE IMPORANT --- THE DRUG COMPANY OR THE CONSUMER ??

The drug policy is now on the anvil. It is now that we can assume the responsibility for putting people's health before the health of the industry. If Indian people have to become healthy, Indian Drug Policy needs to be rational. The choice is ours -- and we must make a decision now.

DR-13

VHAI-AIDAN-NCCDP-RDCC DRUG CONSULTATION
ON
IMPACT OF POLICY CHANGES ON DRUG POLICY AND DRUG USE
26, 27 August 1996

RESEARCH & AWARENESS CAMPAIGN

Drug Hazards in Pregnancy and Lactation

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OBSTETRIC DRUG INFORMATION CELL AT RVHA TO ALERT AGAINST HARMFUL DRUGS IN PREGNANCY

A recent survey by the RVHA of the maternity centers in the city of Jaipur revealed a very high incidence of still births, congenital anomalies and of abnormal pregnancies needing assisted deliveries by caesarean section.One of the possible contributory factor for the incidence of stil births, congenital defects etc is the indiscriminate and indiscreet use of the drugs in pregnancy.

Prescription and intake of drugs in pregnancy needs much higher level of awareness and readily available information about the possible harmful affects of the drugs in pregnancy. In India, where therapeutic preparations marketed run in thousands, it is still more difficult to be aware of the possible harmful content of a specific preparation. Good intentions of physicians to do no harm to conceptus, while prescribing to a pregnant woman for her disease and complaints, are thwarted by the lack of readily available information about the effect on pregnancy of the otherwise commonly prescribed safe drugs to patients. A pregnant lady has no way to check if the prescribed medicines for her ailment are likely to harm her precious child in the womb.

To counter the above mentioned adversities, countries with better developed and more responsive health care systems, run obstetric drug information centers that disseminate the required information to enable rational and non-harmful prescription of drugs in pregnancy. Rajasthan Voluntary Health Association is perhaps the first in the country to attempt to establish such an obstetric drug information cell.

The Obstetric Drug Information Cell at the RVHA has already prepared a computer based data-base of the drugs by their generic and brand names, in term of their reported and recognised (by drug control authorities of India) effects on pregnancy. Lists of the drugs that are either not at all to be given in pregnancy (contraindicated drugs) and those that have to be prescribed with special caution (special precaution) are available both by their generic and brand names. Lists are also available for the use of practitioners of various specialities according to the class of drugs pertaining to their specialities.

The Obstetric Drug Information Cell will provide information to any pregnant lady seeking information about the possibility of any harmful effect, on the child in the womb or the pregnancy, of a drug prescribed to her. The patient may contact, with the prescription, personally or by sending a photocopy of the prescription by post, the Obstetric Drug Information Cell, Rajasthan Voluntary Health Association, C-41, Dev Nagar, Tonk Road, Jaipur-302018, (between 11 AM to 1 PM for personal visit). During this time information will also be available on telephone No.512021.

The Obstetric Drug Information Cell will also mail lists of the contraindicated and the special precaution lists of drugs in pregnancy to various doctors and hospitals, and to any one seeking such lists, subject to the availability of the funds.

OBSTETRIC DRUG INFORMATION CELL

Rajasthan Voluntary Health Association, Jaipur

A large number of drugs, approved as safe in non-pregnant and in non-lactating women, are known to be unsafe in pregnancy and lactation. These drugs are either contraindicated or are to be avoided as far as possible (to be given with caution) because of their known, or potential harmful effect to a pregnant or a lactating mother, or to the child in the womb, or to a child on breast feed.

The drugs that may harm the child or the mother or adversely effect the pregnancy outcome, besides being-

1. drugs taken for pregnancy related conditions might have been taken for
2. treatment of infertility or
3. for an acute or chronic condition from which a pregnant or a lactating woman might suffer.

Potential of harm to foetus is maximum in the first three months of pregnancy. The development of the organs in a foetus takes place in the first three months of pregnancy. The foetus, during this period, particularly from 18th or 60th day of conception, is most vulnerable to the harmful effect of the drugs, which may cause congenital defects leading either to death of the child in the womb and abortion, or birth of a child with defects.

Substantial risk in second trimester. During the next three months, drugs may still cause disorders of growth and function, especially of the brain and the spinal cord, that are mostly non-fatal.

Risk to the child and the mother in late pregnancy. In the last three months of pregnancy, drugs may cause problems in the child birth, or immediately following it, frequently drug related fatal respiratory failure in the new born, more so if the child is born premature. Some drugs may cause excessive bleeding in the mother.

A variety of adverse pregnancy out-comes, such as, abortion, still birth, neonatal death, congenital defects, or defects in functioning of the brain etc, are caused by drugs taken in pregnancy. Rates of such out-comes are much higher in Rajasthan as compared to other parts of our country, and in the country as a whole than in the developed nations. Excessive and indiscriminate prescription and consumption of drugs in pregnancy is one cause of it.

A child on breast feed is vulnerable to the adverse effect of all the drugs taken by the mother that are secreted in the breast milk.

To prevent this large scale medical violence against pregnant women and their innocent children in the womb, an Obstetric Drug Information Cell has been created at the Rajasthan Voluntary Health Association. It will serve the following functions:-

1. Maintain an Obstetric Drug Information Cell with a data base on drugs, by their generic and brand names, about the safety status of these drugs in pregnancy and lactation.

2. The Cell will circulate amongst doctors a list of drugs that are either contraindicated or are to be prescribed with special precaution in pregnancy and a list of similar status of drugs in lactation . This is to enhance the awareness of doctors about the safety standards of these drugs in pregnancy and lactation and to serves as a ready reference.

3. The information at the Cell will be available to the patients who seek information about the safety status of drugs prescribed to them in pregnancy and lactation.

4. The Cell will attempt to persuade the Drugs Control Authorities to ensure printing of easily understandable icon (pictorial depiction) on the drug pack to warn the user that the drug is contraindicated in pregnancy.

5. The Cell will prepare tabulated lists for specialists practitioners showing safety standard of the drugs used in a particular speciality if the patient is pregnant.

THE AUSTRALIAN RISK CATEGORIZATION SYSTEM FOR DRUGS USED IN PREGNANCY

The Anstralian categorization consists of five separate categories:

CATEGORY A	Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.
CATEGORY B	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. As experience of effects of drugs in this category in humans is limited, results of toxicological studies to date (including repro duction studies in animals) are indicated by allocation to one of three subgroups:
GROUP B1	Studies in animals * have not shown evidence of an increased occurrence of fetal damage.
GROUP B2	Studies in animals *are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.
GROUP B3	Studies in animals * have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
CATEGORY C	Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations.These effects may be reversible. Accompanying texts should be consulted for further details.
CATEGORY D	Drugs which have caused, are suspected to have caused, or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
CATEGORY X	Drugs that have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

* Animal studies submitted in support of new drug applications must conform to New Drug Form Guidelines.

Comments on alphabetical pregnancy risk ratings refer to the 1992 ADEC "Medicines in Pregnancy" categorization booklet. These notes are based on that booklet with additional comments and clarification as appropriate.

NOTES ON SAFETY OF VARIOUS DRUGS AND DRUG GROUPS

1 Angiotensin - Converting enzyme (ACE) inhibitors:

Captopril and enalapril are rated as D due to reports of fetal deaths in-utero.

Whilst there is no evidence to suggest that these drugs are teratogenic in humans, it has been suggested that late in pregnancy, these drugs have effects on the fetal renin-angiotensin system, which may be potentially harmful. Therefore, they are best avoided during pregnancy.[1,2,4] For similar reasons the newer drugs Fosinopril and Lisinopril are also rated D in pregnancy.

2 Acyclovir

During pregnancy there is no evidence that acyclovir prevents transmission of genital herpes simplex from mother to fetus and administration during pregnancy is usually contraindicated on theoretical grounds. [5] However, its use should be considered in a primary attack because viraemia occurs and potential damage could result in the infant.[6]

3 Aminoglycosides

Gentamicin, kanamycin, neomycin, tobramycin, amikacin, netilmicin.

Gentamicin and other aminoglycosides are known to cross the placenta. There is evidence of selective uptake of gentamicin by the fetal kidney resulting in cellular damage (probably reversible) to immature nephrons. Eighth cranial nerve damage has also been reported following in-utero exposure to some of the aminoglycosides. Because of their chemical similarity, all aminoglycosides must be considered potentially nephrotoxic and ototoxic to the fetus. It should also be noted that therapeutic blood levels in the mother do not equate with safety for the fetus.[5]

4 Amiodarone

Because of the long half-life of amiodarone and its major metabolite, and the potential to cause abnormal thyroid function and bradycardia in the fetus, its use is probably

best avoided in the three months before and throughout the duration of pregnancy. Where exposure of the fetus is unavoidable, thyroid function (including TSH) should be assessed promptly in the newborn infant. [29]

5 Anticonvulsants

The risk of a mother with epilepsy giving birth to a baby with an abnormality is about three times that of the normal population. Some of this risk is due to the anticonvulsant drugs taken. Mothers, taking more than one anticonvulsant drug, might have a higher risk of having a baby with a malformation than mothers taking one drug. Phenytoin sodium, taken during pregnancy, has been associated with distinctive craniofacial abnormalities, mental and growth deficiency and less frequently, oral clefts and cardiac anomalies. This clinical pattern is sometimes called the 'fetal hydantoin syndrome'.

Sodium valproate (valproic acid), if taken in the first trimester of pregnancy, is suspected of causing an increased risk of neural tube defects (especially spina bifida) in the exposed fetus. Women taking sodium valproate (valproic acid), who become pregnant, should be encouraged to consider routine ultrasound and amniocentesis for prenatal diagnosis of such abnormalities. [7] Alternatively, pre-pregnancy genetic counselling is advised.

In practice, if a patient is stabilized on anticonvulsants prior to pregnancy, and the patient is counselled as to the potential increase in overall risk, and wishes to continue with the pregnancy, this therapy is usually continued for that patient throughout the pregnancy, with close serum monitoring where this is possible. It has also been suggested that folate supplementation may reduce the potential for teratogenic outcome. This is in line with the general consensus of advice for these patients during pregnancy, [7,8]. We would strongly disagree with the D rating for clonazepam, and would place it at a B3 rating since there is no epidemiological evidence of teratogenicity with the use of benzodiazepines other than studies of small numbers with inconsistent results. For other fetal effects of benzodiazepines, please refer to benzodiazepine notes [8,11,12].

6 Antihistamines and Anti-emetics.

The Australian categorisation differentiates between some antihistamines and others, on their chemical basis, namely that some are phenothiazine derivatives, and that phenothiazines used late in pregnancy, have caused prolonged extra-pyramidal disturbances in the child.

Phenothiazines are given a C categorisation, whilst meclozine, dexchlorpheniramine, and the antiemetic metoclopramide are given an A categorisation. The antihistamines azatadine, methdilazine and terfenadine are given a B2 rating.

Doxylamine is no longer available as a single ingredient, but is contained in a combination product with paracetamol and codeine. This combination product-Mersyndol (Merrell Dow) may be regarded as safe for short-term use during pregnancy. Astemizole is given a C rating because of its long (4-month) elimination half-life. Because of the potential to accumulate, it should probably be avoided during pregnancy. In practice, we would not differentiate between the older antihistamines and anti-emetic preparations, but agree that there may be the theoretical possibility of extra pyramidal effects from phenothiazines, when used late in pregnancy. There are insufficient data on loratadine and terfenadine use in pregnancy. Therefore they are not recommended for use at this stage.

7 Antimalarial Preparations

The antimalarial preparation pyrimethamine is given a B3 categorisation. Chloroquine and related substances are given a D categorisation. The antimalarial combination of pyrimethamine and dapsone is given a B3 rating whilst pyrimethamine and sulfadoxine is given a C rating.

The ADEC categorisation booklet notes that the use of chloroquine and related drugs in the prophylaxis of malaria is accepted because the small risk to the fetus with the low doses is outweighed by the benefits to the mother and the fetus.

The difference between pyrimethamine-dapsone and pyrimethamine-sulfadoxine is that sulfadoxine, and other long acting sulphonamides, may cause kernicterus in babies during the first month of life, by displacing bilirubin from plasma albumin.

The difference in the ratings reflects, fairly well, the advice that we give, with regard to these preparations, namely that chloroquine is regarded as being safe if it is used for prevention of malaria, and that the pyrimethamine-dapsone combination is not established as being as safe as chloroquine but may need to be given if exposure to chloroquine-resistant strains of malaria cannot be avoided. Where this is the case, folate supplementation may be used, to reduce the theoretical potential for teratogenic outcome [9]. Mefloquine has been used later in pregnancy. Not recommended for use in the first trimester, as limited teratogenicity data are available.

Pyrimethamine-sulfadoxine is generally not recommended during pregnancy.

8 Antithyroid Drugs

Antithyroid agents may cause congenital goitre by inhibiting thyroxine synthesis in the fetus. During pregnancy these products should therefore only be used after carefully weighing the mother's needs against the risk to the fetus. Propylthiouracil is usually preferred to carbimazole because of suggestions of potential congenital skin lesions, arising from the use of carbimazole and related drugs during pregnancy [10]

9 Appetite Suppressants

Fenfluramine is rated B2 and others in the group are rated B3. There are no good epidemiological data on safety of these preparations during pregnancy. They are not usually recommended for use during pregnancy.

10 Analgesics (including Narcotics)

The opioid analgesics are given a C categorisation on the basis that narcotic analgesics may cause respiratory depression in the newborn infant. It is stated that during the last two to three hours before expected delivery, these preparations should only be used after weighing the needs of the mother against the risk to the fetus. This reflects the reality of the risk-benefit ratio of these preparations, since morphine, pethidine and other narcotics have been used in obstetric practice for many years, with the full realisation that there may be the potential for respiratory depression. Codeine is given a category A rating. The narcotic antagonist naloxone is rated A. Paracetamol is regarded as safe to use during pregnancy and is rated A.

11 Barbiturates

Amylobarbitone, pentobarbitone, methylphenobarbitone

Barbiturates cross the placenta and appear in the fetus. After prolonged continuous usage during a large part of pregnancy, they give rise to hypotension, reduced respiratory function and hypothermia in the newborn child. Continuous treatment during pregnancy and administration during labour should therefore be avoided.

12 Benzodiazepines

These drugs cross the placenta and appear in the fetus and may, after continuous administration during a large part of pregnancy, give rise to hypotension, reduced respiratory function and hypothermia in the newborn infant. Withdrawal symptoms have been reported with this class of drugs. Continuous treatment during pregnancy and administration of high doses in connection with delivery should therefore be avoided. Short-term use, such as single night-time hypnotic dosage, is not considered to be a problem.

13 Beta-adrenergic Blocking Agents

Beta-adrenergic blocking agents are rated as C, because of their potential to cause bradycardia in the fetus and the newborn. Labetalol, metoprolol, and oxprenolol have been successfully used, and have not demonstrated adverse effects in this regard [10,11,12,13,14]. However, there have been some studies which have shown lower

birthweight in the infants of atenolol-treated women compared with alternative treatments including labetalol. On that basis, the combined alpha and beta blocker, labetalol may be a preferred option, to using beta blocking agents.

14 Calcium-channel Blockers

Verapamil and nifedipine are rated C, due to their potential for fetal hypoxia. The Swedish category for verapamil is A. There is sufficient evidence to suggest that verapamil may be safely used in pregnancy and it would be more worthy of a B1 rating [15].

15 Corticosteroids

In animal experiments, corticosteroids have been found to cause malformations of various kinds (cleft palate, skeletal malformations). These findings do not seem to be relevant to humans. Reduced placental and birth weight have been recorded in animals and humans after long-term treatment.

Systemic corticosteroids, with the exception of replacement doses, are listed as C category, since there is obviously the possibility of adrenal cortex suppressions in the newborn after long-term treatment.

Corticosteroids by inhalation have been widely used for many years without adverse effects in pregnancy, up to 1600mcg daily

The short-term use of antepartum corticosteroids for the prevention of respiratory distress syndrome, when warranted, does not seem to pose a risk.

It is also documented that internal pulmonary oedema has been reported with tocolysis and fluid overload.

Topical steroids, including fluorinated steroids, are listed as Category A. They are safe for short-term use on unbroken skin for the treatment of appropriate dermatological conditions.

16 Cyproterone

Cyproterone carries the potential for feminization of the male fetus, and therefore should be avoided during pregnancy.

17 Thiazides and other diuretics

Thiazides, related diuretics and loop diuretics enter the fetal circulation and may cause electrolyte disturbances. Neonatal thrombocytopenia has been reported with thiazides and related diuretics. Loop diuretics, like frusemide and bumetanide are probably also associated with this risk. During the latter part of pregnancy, products

of this type should therefore only be given on sound indications, and then in the lowest effective dose.

18 Haloperidol

Although there have been isolated case reports of birth defects following fetal exposure to haloperidol in combination with other drugs, no definite cause and effect relationship can be confirmed.

19 Anticoagulants

Coumarin derivatives, including warfarin, are rated D. We agree with this rating, due to their teratogenic potential as well as the potential for haemorrhage.

Heparin is also given a C rating due to "increased incidence of human loss and prematurity associated with haemorrhage". The Swedish category for heparin is B2. We disagree with the C rating, as we believe that heparin, effectively monitored, has been safely used for prophylaxis and treatment during pregnancy over several years world-wide. We would place its rating at B1. This is in line with clinical experience and reviews on the subject [16,17]. Obviously, with high-dose use of heparin during pregnancy, considerations such as bone demineralization and other well known potential adverse effects on the mother, need to be considered.

20 Lithium

Lithium enters the fetal circulation and cases of disturbances of thyroid function of the newborn infant have been reported. Available data also indicate that lithium during pregnancy may cause malformations of the cardiovascular system.

21 Non-steroidal Anti-inflammatory Drugs

All drugs in this category are given a C rating, on the basis of their inhibitory effect on prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the fetal ductus arteriosus. When given at term, they may prolong labour and delay parturition [18,19].

Continuous treatment with non-steroidal anti-inflammatory drugs during the last month of pregnancy should only be given on sound indications.

Generally speaking, indomethacin, ibuprofen, diclofenac and similar preparations are not withheld during pregnancy. Aside from the precautions noted above, they do not present other risks to the infant .

Aspirin is given a C rating, due to its potential for inhibition of prostaglandin synthesis, which may cause premature closure of the fetal ductus arteriosus, its

potential of prolonging labour, and its tendency to increase bleeding capacity in the newborn [20,21,22]. Aspirin-containing products should, therefore, be avoided in late pregnancy.
Low-dose aspirin has been advocated for prevention of pre-eclampsia. However, if used, it should be discontinued 1-2 weeks prior to expected date of delivery, because of uncertainty as to the safety of low-dose aspirin and epidural anaesthesia.
The ADEC Classification booklet also notes that animal studies have shown aspirin to cause birth defects in animals, but there is no conclusive evidence that aspirin causes malformations in humans. This is in accordance with our own recommendations. It is to be noted that paracetamol is listed as a category A preparation, as it has not demonstrated any direct toxicity or teratogenicity when used during pregnancy.

22 Nitrofurantoin

Nitrofurantoin was originally given a C rating, in the 1989 classification, on the basis of the caution required when given at term or to infants under one month, because of the theoretical possibility of producing haemolytic anaemia due to immature enzyme systems in the early neonatal period. In fact, this has not been reported to have occurred in practice [26]. It is placed in the A category in the 1992 classification.

Nitrofurantoin has been quite widely and safely used throughout pregnancy for over thirty years. In both the United States of America and Sweden it is placed in the category equivalent to category A. An assessment of the literature confirms the view that the rate of haematological reactions is very low (around 0.0004% of doses given). We would, therefore, agree with the "A" categorization [27,28].

23 Sex Hormones, including Oral Contraceptives

Animal studies have shown that high doses of progestogens can cause masculinization of the female fetus. Because of this virilising effect on the fetus, they are rated D. The results from these experiments in animals do not seem to be relevant to humans, in the low doses used in contraceptives.

Obviously, the rating with respect to these hormones is of most relevance retrospectively, in the case of inadvertent use of a particular drug in early pregnancy, as these preparations would not normally be prescribed during pregnancy, if it were known that the patient was pregnant. In this context, low dose progestogens should probably be a B1 or B2 rating. (See also comments following, with regard to oral contraceptives.)

We would also advocate individual counselling where appropriate, to the effect that the inadvertent use of allylestramol, dydrogesterone or medroxyprogesterone in early pregnancy, should not be regarded as a reason for interruption of pregnancy, as the evidence suggests that the actual risk of virilization is minimal. Anabolic steroids are rated D due to their potential for virilising effects on the fetus. Danazol has also demonstrated an androgenic effect on the fetus in several reported cases.
Stilboestrol is rated X.

Oral contraceptives (again, obviously inadvertently used in early pregnancy) are rated B3. This is a reasonable rating, since there is no evidence that intake of oral contraceptives during pregnancy represents an increased risk to the fetus. It should be noted that the studies, indicating links between oral contraceptives and limb reduction deformities, were all carried out during the years when oral contraceptives contained high-strength oestrogens and progestogens, prior to the introduction of the more modern low-strength preparations, and progestogen-only preparations in the early 1980's. [2124] Indeed, early formulations, contained in some cases, 10 to 20 times the equivalent steroid content compared to modern formulations.

24 Oral Hypoglycaemic Agents

In animal studies birth defects have been demonstrated. They should therefore not be used during pregnancy but should be replaced by insulin.

25 Phenothiazines

Fluphenazine, perphenazine, chlorpromazine, pericyazine, thioridazine, trifluoperazine, promazine, prochlorperazine.

When given in high doses during later pregnancy, phenothiazines have caused prolonged extrapyramidal disturbances in the child.

26 Vitamin A

Excess vitamin A may cause birth defects. Women should consider their dietary intake of vitamin A before taking supplements. The Australian diet usually contains the recommended daily allowance of 2500 IU.

27 Rifampicin

Bleeding, attributable to hypoprothrombinaemia, has been reported in newborn infants and in mothers after the use of rifampicin during late pregnancy. In animal experiments, rifampicin, given during organ development, has caused skeletal malformations. If rifampicin is used during the last few weeks of pregnancy, vitamin K should be given to the mother and the newborn infant.

28 Sulphonamides

Sulphonamides may cause kernicterus in babies during the first month of life by displacing bilirubin from plasma albumin. Sulphonamides should therefore be avoided as far as possible during the last month of pregnancy.
The rapidly-excreted sulphonamide, sulphamethizole, may be regarded as being safe for use in pregnancy, bearing in mind the concern about the use of sulphonamides as a group late in pregnancy.

29 Tetracyclines

During the period of mineralisation of a child's teeth (the second and third trimester of pregnancy, the neonatal period and the first 8 years of life) tetracyclines may induce hypoplasia of the enamel and discolouration of the teeth. Tetracyclines also accumulate in the growing skeleton. These products should be avoided during the second and third trimesters of pregnancy.

30 Tricyclic antidepressants

Amitriptyline, desipramine, imipramine, trimipramine, nortriptyline, opipramol, protriptyline, clomipramine.

Tricyclic antidepressants have not been shown to be associated with an increased incidence of birth defects. However, there is evidence of interference with central monoamine neurotransmission in rats. Care should be taken that there are sound indications for the use of these antidepressants in pregnancy.

31 Vaccines

The ADEC categorisation booklet states:

"Women of child-bearing age should be tested prior to pregnancy. All seronegative women of child-bearing age, provided they are not pregnant, should be offered rubella vaccine. As the virus in rubella vaccine can cause fetal infection, it is desirable that the vaccine should not be administered to any women who may be pregnant. Those administering the vaccine should be careful to instruct women to whom it is given that they should not become pregnant for at least two full menstrual cycles. However, to date, there have not been any rubella-like birth defects in the live born infants (about 400) of seronegative mothers vaccinated during or just before pregnancy. Based on this experience, rubella vaccination during pregnancy need not be the reason to recommend interruption of pregnancy. The final decision must be made by the patient and her physician."

We agree with these comments, and they are supported by the recommendations of the United States Practices Advisory Committee of the Center for Disease Control, U.S.A.(25). This group further states that "both yellow fever vaccine and oral polio vaccine can be given to pregnant women at substantial risk of exposure to infection. When vaccine is to be given during pregnancy, waiting until the second or third trimester to minimise any concern over teratogenicity is a reasonable precaution" [25].

Although adverse effects on the fetus have not been reported, oral poliomyelitis vaccine should not normally be given to women during the first four months of pregnancy unless there are compelling reasons.

There is no convincing evidence of risk to the fetus from immunisation of pregnant women using inactivated virus vaccines, bacterial vaccines or toxoids [29].

32 Penicillamine

Penicillamine can cause cutis laxa in the human fetus [29].

33 Bismuth Subnitrate

Bismuth is a heavy metal which crosses the placenta. Although there have been no reports of adverse effects in the human fetus, use of this preparation is not recommended during pregnancy.

34 Sodium Nitroprusside

Sodium nitroprusside is used in high risk situations and there may be additional hazards associated with the drug. It crosses the placenta. Short term use for control of hypertensive crises may be safe provided the maternal pH and cyanide levels are monitored.

35 Hydralazine

Hydralazine is used for treating hypertensive crises, where rapid blood pressure contol is required. However, it is rated C, on the basis that fetal distress and arrhythmia have been reported following intravenous use late in pregnancy.

36 Metronidazole

Reviewing all the available animal and human data on the safety of metronidazole in pregnancy, we may conclude that epidemiological and clinical data accumulated, over a period of 30 years, has failed to show evidence of teratogenicity. With regard to mutagenicity, experimentally, chemicals of a class to which metronidazole belongs, may be shown to be mutagenic. However, there is no evidence that metronidazole has this effect in human usage.

Metronidazole is classified as B2 by the ADEC "Medicines In Pregnancy" classification system.

Therefore, if metronidazole is the drug of choice, for a particular infection during pregnancy, review of available evidence regarding its safety during pregnancy suggests that it may be safely used.

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DRUG REFERENCE CHART ACCORDING TO MIMS

GENERIC NAME	PREGNANCY		LACTATION	
	SP	CI	SP	CI
5 AMINOSALICYLICACID		•		•
5 FLUOROURACIL		•		
ACEBUTOLOL	•			
ACETAZOLAMIDE	•			
ACYCLOVIR	•			•
ADRENOCHROME	•			
ALBENDAZOLE		•		•
ALFACALCIDOL	•		•	
ALLOPURINOL	•			•
ALLYLOESTRENOL	•			
ALPRAZOLAM		•		•
AMANTADINE		•		•
AMIKACIN		•		
AMILORIDE	•		•	
AMINEPTINE		•	•	
AMIODARONE		•		•
AMITRIPTYLINE	•		•	
AMLODIPINE		•	•	
AMODIAQUINE	•			
AMOXAPINE	•		•	
AMOXYCILLIN		•		
AMPHOTERICIN B	•		•	
AMPICILLIN C SULBACTAM SOD	•		•	
AMRINONE	•		•	
AMYLOBARBITONE		•		•
ANALGIN	•			•
ANTHRAQUINONES	•			•
APROTININ	•			•
ASPIRIN		•		
ASTEMIZOLE		•		•
ATENOLOL & NIPEDIPINE	•			
ATRACURIUM		•		
AURANOFIN	•			
AZATHIOPRINE	•			
AZITHROMYCIN	•		•	
BETAMETHASONE	•			•
BETAXOLOL	•			
BEZAFIBRATE		•		•
BISOPROLOL		•	•	
BLEOMYCIN	•		•	
BROMOCRIPTINE	•		•	
BUMOCRIPTINE	•		•	
BUMETANIDE	•		•	
BUPRENORPHINE		•		
BUSPIRONE		•		•
BUSULPHAN 31 HAL CINONIDE P		•		
CAPTOPRIL		•		•
CARBAMAZEPINE	•		•	

GENERIC NAME	PREGNANCY		LACTATION	
	SP	CI	SP	CI
CARBIDOPA & BENSERAZIDE			•	•
CARBIMAZOLE	•			•
CARBOPROST		•		•
CARISOPRODOL	•	•		
CEFACLOR	•		•	
CEFADROXIL	•		•	
CEFAZOLIN SODIUM	•			
CEFOPERAZONE SOD	•		•	
CEFOTAXIME	•		•	
CEFLAZIDIME	•			
CEFLAZIDIME	•		•	
CEFLRIAXONE	•			
CEFUROXIME		•		•
CENTCHROMAN	•			
CEPHALEXIN	•			•
CETRIZINE DI HCL	•			•
CHLORAMBUCIL		•		•
CHLORAMPHENICOL	•		•	
CHLORDIAZEPOXIDE	•		•	
CHLORMEZANONE		•		
CHLOROQUINE		•		
CHLORPROPAMIDE	•		•	
CHLORTHALIDONE		•	•	
CICLOPIROX OLAMINE	•		•	
CIMETIDINE	•			
CINNARIZINE	•		•	
CIPROFLOXACIN		•	•	
CISAPRIDE		•		•
CISPLATIN	•		•	
CLEMASTINE FUMARATE	•			
CLIDINIUM		•	•	
CLINDAMYCIN	•			
CLOBETASOL ACETATE	•			
CLOBETASOL PROPIONATE	•			
CLOBETASONE -17 BUTYRATE	•			
CLOFAZIMINE	•		•	
CLOMIPHENE		•		
CLOMIPRAMINE	•			•
CLONAZEPAM		•		•
CLONODINE	•		•	
CLOPAMIDE		•		•
CLOTRIMAZOLE		•		
CO-TRIMOXAZOLE		•		•
COLISTIN				•
COUMARINS & INDANEDIONES	•		•	
CYCLOPHOSPHAMIDE		•		•
CYTOSINE ARABINOSIDE		•	•	
D-PENICILLAMIN		•		•
DANOZOL		•		•

DRUG REFERENCE CHART ACCORDING TO MIMS

GENERIC NAME	PREGNANCY		LACTATION	
	SP	CI	SP	CI
DEXAMETHASONE		•		
DEXFENFLURAMINE		•		•
DEXTROPROPOXYPHE	•			
DIAZEPAM	•		•	
DICLOFENN SODIUM		•		•
DICYCLOMINE	•			•
DIETHYL CARBAMAZINE CITRATE	•	•		
DIENOESTROL		•		
DILAZEP	•		•	
DILOXANIDE FUROATE	•		•	
DILTIAZEM		•	•	
DIMENHYDRINATE		•		
DIPHENOXYLATE	•			•
DIPHENYLMETHANES	•			
DIPYRIDAMOLE	•		•	
DISOPYRAMIDE	•		•	
DISULFIRAM		•		•
DOMPERIDONE		•		
DOTHIEPIN HCL		•	•	
DOXEPIN	•		•	
DOXORUBICIN		•		•
DOXYCYCLINE		•		•
ECONAZOLE	•			
ENALAPRIL MALEATE		•	•	
EPHEDRINE	•			•
ERGOTAMINE		•	•	
ERYTHROMYCIN	•			
ESTROGENS		•	•	
ETHAMBUTOL	•		•	
ETHAMSYLATE		•	•	
ETHINYLESTRADIOL		•		•
ETHOSUXIMIDE		•		•
ETOPOSIDE		•		•
FAMOTIDINE	•		•	
FELODIPINE		•		•
FENFLURAMINE		•		•
FENOPROFEN		•		•
FLUCONAZOLE	•			•
FLUCINOLONE ACETONIDE			•	
FLUOCORTOLONE			•	
FLUOXETINE HCL	•			•
FLUPHENAZINE		•		
FLURAZEPAM		•	•	
FLURBIPROFEN	•			•
FRUSEMIDE	•		•	
FTORAFUR		•		
FURAZOLIDONE	•		•	
GALLAMINE		•		
GEMFIBROZIL	•			•

GENERIC NAME	PREGNANCY		LACTATION	
	SP	CI	SP	CI
GENTAMICIN	•			
GLIBENCLAMIDE		•		•
GLICLAZIDE		•		•
GLIPIZIDE		•		•
GLUCAGON	•		•	
GLYCERYL TRINITRATE	•		•	
GLYCOPYRROLATE	•		•	
GRISEOFULVIN		•	•	
HALCINONIDE			•	
HALOPERIDOL				•
HEPARIN	•		•	
HOMATROPINE		•		•
HYDANTOINS		•	•	
HYDRALAZINE/DI HYDRALAZINE	•	•		
HYDROCHLOROTHIAZIDE	•			
HYDROCORTISONES SOD SUCCINATE	•			
HYOSCINE BUTYLBROMIDE	•		•	
IBUPROFEN	•		•	
IFOSFAMIDE		•		•
IMIPRAMINE	•		•	
INDAPAMIDE	•		•	
INDOMETHACIN	•		•	
INSULINS	•			
IODINE	•			•
ISOSORBIDE 5 MONONTRATE	•		•	
KANAMYCIN		•		
KETAMINE		•		
KETOCONAZOLE		•		•
KETOPROFEN	•			•
KETOCONAZOLE	•		•	
KETOPROFEN		•		•
KETOTOLAC TROMETHAMINE	•		•	
KETOTIFEN		•		•
LABETALOL	•		•	
LANSOPRAZOLE		•		
LEVAMISOLE AND TETRAMISOLE	•		•	
LEVODOPA		•		•
LIDOCAINE	•		•	
LINCOMYCIN	•		•	
LISINOPRIL		•		•
LITHIUM		•		•
LOMEFLOXACIN	•		•	
LOPERAMIDE	•		•	
LORATADINE	•			•
LORAZEPAM	•		•	
LOXAPINE	•			•
LYNESTRENOL		•	•	
MEBENDAZOLE		•		•
MEBEVERINE				•

DRUG REFERENCE CHART ACCORDING TO MIMS

GENERIC NAME	PREGNANCY		LACTATION	
	SF	CI	SF	CI
MELPHALAN		•		•
MENOTROPHIN		•		
MERCAPTOPURINE		•		•
METFORMIN		•		•
METHOCARBAMOL	•			
METHOTREXATE		•		•
METHYLDOPA			•	
METHYL TESTOSTERONE		•		•
METOCLO*RAMIDE		•		
METRONIDAZOLE	•			•
MEXILETINE	•			•
MIANSERIN	•			•
MICONAZOLE	•		•	
MINOCYCLINE		•		•
MINOXIDIL	•			•
MITOMYCIN-C		•		•
MOMETASONE FUROATE	•		•	
MUSTINE HCL		•		•
NALIDIXIC ACIDL	•		•	
NAPROXEN		•	•	
NEOMYCIN		•	•	
NETILMICIN	•			
NICERGOLINE		•		•
NICLOSAMIDE	•			
NIFEDIPINE	•			•
NIMODIPINE	•			•
NITRAZEPAM	•		•	
NITRENDIPINE	•			•
NITROFURANTOIN				•
NORETHISTERONENANTATE		•	•	
NORFLOXACIN		•		•
NORTRITTYLINE	•			•
NYSTATIN	•			
OESTROGEN		•		•
OFLOXACIN		•		•
OMEPRAZOLE	•			•
ONDANSETRON	•			•
ORPHENADRINE	•		•	
OXAZEPAM		•		•
OXPRENOLOL	•		•	
OXYMETAZOLINE	•		•	
OXYPHENBUTAZONE	•			
OXYTETRACYCLINE	•			•
PANCURONIUM	•			
PEFLOXACIN		•		•
PENFLURIDOL	•		•	
PENICILLIN - G			•	
PENTAZOCINE	•		•	
PENTOXIFYLLINE	•			•

GENERIC NAME	PREGNANCY		LACTATION	
	SF	CI	SF	CI
PERINODO*RIL		•		•
PHENAZO*YRIDINE	•		•	
PHENOBARBITONE	•		•	
PHENYLBUTAZONE	•			
PHENYLE*HRINE		•	•	
PIMOZIDE	•			•
PINDOLOL	•			•
PIRACETAM		•		
PIROXICAM		•		•
POLYMYXIN B	•			
PRALIDOXIME CHLORID	•		•	
PRAZIQUANTEL			•	
PRAZOSIN	•		•	
PREDNISOLONE	•			•
PROBENECID	•			
PROCAINAMIDE	•			•
PROCHLORPERAZINE	•		•	
PROMETHAZINETHEOCLATE		•		•
PROPANTHELINE	•		•	
PROPRANOLOL	•		•	
PYRANTEL PAMOATE	•			•
PYRAZINAMIDE		•		•
QUINIDINE	•		•	
RAMIPRIL		•		•
RANITIDINE	•		•	
RIBAVIRIN		•		•
ITASOXACLS				
PXOXATIDINE ACTTATE				
ROXITHROMYCIN				
SALBUTAMOLE	•			
SECNIDAZOLE		•		
SELEGILINE	•		•	
SISOMYCIN		•		
SOD CROMOGLYCATE	•		•	
SOD. NITROPRUSSIDE	•		•	
SOTALOL			•	
SPIRAMYCIN	•			•
SPIRONOLACTONE	•			
STRPTOKINASE	•			
SUCCINYLCHOLINE CHL.	•			
SUCRALFATE				
SULFADOXINEPYR				
IME-THIAMINE				
SULFAMOXOLE				
SULPHACETAMNIDE	•			
SOD				
TAMOSIIFEN		•	•	
TENOXICAM				
TERAZOSIN				

DRUG REFERENCE CHART ACCORDING TO MIMS

GENERIC NAME	PREGNANCY		LACTATION	
	SF	CI	SF	CI
TERFENADINE		•	•	
TESTOSTERONE		•		•
TETRACYCLINE		•	•	
THYROXINE SODIUM			•	
THIO-TEPA				•
TICLOPIDINE				
TIMOLOL MALEATE	•			
TINIDAZOLE	•			•
TOLBUTAMNIDE		•		
TRAMADOL HCL	•		•	
TRAZODONE	•			•
TRIAMTERENE				
TRICLOFOS SODIUM				
TRISLUOPERAZINE				
TRIXDUOPERIDOL				
TRIFLUPEOMAZINE				
TRIMETHOPRIM		•		•
SULPHA				
TRIMIPRANINE				
VALETHAMATE				
VANCOMYC IN				
VERAPAMIL				

Gastrointestinal Drug Use in Pregnancy

Category A	Group B1	Group B2	Group B3	Category C	Category D	Category X	Unlisted
antacids	cimetidine	bismuth subcitrate	loperamide	dexamethasone	doxycycline	misoprostol	azathioprine
bisacodyl	cisapride	cholestyramine	nizatadine	diphenoxylate	neomycin		dicyclomine
cascara	famotidine	domperidone	omeprazole	hydrocortisone			lactulose
codeine phosphate	ondansetron	hyoscine salts	spironolactone	interferons			mebeverine
dimenhydrinate	ranitidine	hyoscine-N-butylbromide		mesalazine			olsalazine
docusate	sucralfate	hyoscyamine		octreotide			pancrelipase
frangula		metronidazole		prednisolone			peppermint oil
meclozine		phenolphthaleine		prochlorperazine			polyethylene glycol
metoclopramide		propantheline		promethazine			pyridoxine
senna, sennosides		vasopressin					sorbitol
							ursodeoxycholic acid
sulfasalazine							vitamin D

ANTIMICROBIAL DRUG USE IN PREGNANCY

	CATEGORY A	GROUP B1	GROUP B2	GROUP B3	CATEGORY C	CATEGORY D
aminoglycosides						amikacin gentamicin netilmicin tobramycin
antifungals	nystatin (topical)	miconazole	amphotericin	ketoconazole fluconazole flucytosine griseofulvin		
antimalarials				mefloquine pyrimethamine- dapsone	pyrimethamine- sulfadoxine	chloroquine quinine
anti-tuberculous	ethambutol isoniazid		pyrazinamide		rifampicin clofazimine	
cephalosporins	cephalexin cephalothin	other cephalosporins				
macrolides	clindamycin erythromycin lincomycin	roxithromycin				
penicillins	amoxycillin ampicillin benzathine penicillin benzylpenicillin cloxacillin methicillin penicillin V	amoxycillin/ potassium clavulanate ticarcillin flucloxacillin piperacillin aztreonam procaine penicillin				
quinolones	nalidixic acid			ciprofloxacin norfloxacin		
sulphonamides/ trimethoprim			dapsone	trimethoprim	co-trimoxazole sulphadizine sulphadoxine sulphamethoxazole	
miscellaneous	hexamine nitrofurantoin	spectinomycin praziquantel	acyclovir metronidazole vancomycin	mebendazole thiabendazole tinidazole zidovudine	chloramphenicol fusidic acid	tetracyclines

*Based on Medicines in Pregnancy, 2nd ed. Australian Drug Evaluation Committee, Australian Government Publishing Service, Canberra, 1992.

RESPIRATORY DRUG USE IN PREGNANCY

CATEGORY A	GROUP B1	GROUP B2	GROUP B3	CATEGIRY C	CATEGORY D	CATEGORY X	UNLISTED
adrenaline	amoxycillin/	calcitonin	amantadine	alprazolam	cyclophosphamide		astemizole
aminophylline	potassium clavulanate	dapsone	beclomethasone	amitriptyline	doxycycline		azathioprine
amoxycillin		metronidazole	ciprofloxacin	aspirin	gentamicin		budesonide
benzylpenicillin	cefaclor	pseudoephedrine	flunisolide	chloramphenicol	medroxy-		dalteparin
cephalothin	cefotaxime	pyrazinamide		co-trimoxazole	progesterone		enoxaparin
clindamycin	ceftriaxone	terfenadine		dexamethasone	mustine hydrochloride		loratadine
codeine	flucloxacillin	vancomycin		diazepam	tobramycin		methoxamine
diphenhydramine	ipratropium			heparin	warfarin		oxymetazoline
erythromycin				hydrocortisone			pamidronate
ethambutol				morphine			roxithromycin
fenoterol				oxazepam			salmeterol
isoniazid				pentamidine			streptomycin
orciprenaline				pethidine			tissue plasminogen activator
paracetamol				prednisolone			tramazoline
phenoxymethyl-penicillin				rifampicin			
pholcodeine				streptokinase			
procaine penicillin							
salbutamol							
sodium							
cromoglycate							
terbutaline							
theophylline							

Table 6

Cardiovascular Drug Use in Pregnancy*

Category A	Group B1	Group B2	Group B3	Category C		Category D	Category X	Unlisted
adrenaline	isosorbide dinitrate	acetylcysteine	clonidine	amiloride	indomethacin	captorpril		adenosine
atropine	mexiletine	cholestyramine	dopamine	amiodarone	labetalol	enalapril		dalteparin
digoxin	oestradiol valerate	colestipol	flecainide	amlodipine	metolazone	fosinopril		enoxaparin
isoprenaline	probucol	disopyramide	gemfibrozil	aspirin	metoprolol	lisinopril		n-3 fish oil
lignocaine	ticlopidine	dobutamine	spironolactone	atenolol	minoxidil	medroxypro-		concentrate
methyldopa		glyceryl trinitrate		betamethasone	morphine	-gesterone acetate		sodium
		isosorbide mononitrate		bretylium	nifedipine	nicotine		bicarbonote
		nicotinic acid		bumetanide	nimodipine	perindopril		rt-PA
		perhexilene		chlorothiazide	oxprenolol	phenytoin		
		prazosin		diazepam	pravastatin	quinapril		
				diazoxide	promethazine	ramipril		
				diltiazem	quinidine bisuplhate	trandolapril		
				esmolol	simvastatin			
				felodipine	sodium			
				frusemide	nitroprusside			
				heparin	sotalol			
				hydralazine	streptokinase			
				hydrochloro- -thiazide	triameterence			
				hydrocortisone	verapamil			
				indapamide	warfarin			

* *Based on "Medicines in Pregnancy", Australian Drug Evaluation Committee, Australian Government Publishing Services, Canberra, 1992, Copyright, Commonwealth of Australia, Reproduced with permission.*

DRUGS CONTRA INDICATED IN PREGNANCY BY GENERIC NAME ACCORDING TO CIMS

S.No.	GENERIC NAME	S.No.	GENRIC NAME
1	5-FLUOROURACIL	2	ACETAZOLAMIDE
3	ACETYL SALICYLIC ACID	4	ALBENDAZOLE
5	ALPRAZOLAM	6	AMANTADINE
7	AMIKACIN	8	AMINEPTINE
9	AMINOCAPROIC ACID	10	AMIODARONE
11	AMLODIPINE	12	AMOXYCILLIN
13	AMYLOBARBITONE	14	ASPARAGINASE(L)
15	ASPIRIN	16	ASTEMIZOLE
17	ATRACURIUM	18	AY5-AMINOSALICYLIC ACID
19	AZATADINE MALEATE	20	BENZOYL PEROXIDE
21	BETAXOLOL	22	BEZAFIBRATE
23	BUPRENORPHINE	24	BUSPIRONE
25	CAPTOPRIL	26	CARBIDOPA
27	CARBIDOPA & BENSERAZIDE	28	CARBINOZAMINE MALEATE
29	CARBOCISTEINE	30	CARBOPROST
31	CEFAZOLIN	32	CHLORAMBUCIL
33	CHLORAMPHENICOL	34	CHLORDIAZEPOXIDE
35	CHLORPROPAMIDE	36	CHLORTHALIDONE
37	CIPROFLOXACIN	38	CISAPRIDE
39	CISPLATIN	40	CLEFAZIMINE
41	CLEMIZOLE	42	CLOFAZIMINE
43	CLOMIPHENE	44	CLOMIPRAMINE
45	CLOPAMIDE	46	CODEINE
47	CYCLOPHOSPHAMIDE	48	CYTOSINE ARABINOSIDE
49	DANAZOL	50	DEMOECLOCYCLINE
51	DEXAMETHASONE	52	DEXTROPROPXYPHENE
53	DIAZEPAM	54	DICLOFENAC SODIUM
55	DIENOESTROL	56	DIETHYL CARBAMAZINE CITRATE
57	DILOXANIDE FUROATE	58	DIMENHYDRINATE
59	DIPHENHYDRAMINE	60	DIPHENYL HYDANTOIN
61	DIPHENYL PYRALINE	62	DISMUTH SUBCITRATE
63	DISULFIRAM	64	DOMPERIDONE
65	DOTHIEPIN HCL	66	DOXORUNICIN
67	DOXYCYCLINE	68	DYDROGESTERONE
69	EMBRAMINE	70	ENALPRIL MALEATE
71	ERGOTAMINE TARTARATE	72	ESTROGENS (CONJUGATED)
73	ETHAMSYLATE	74	ETHINYL ESTRADIOL
75	ETOPOSIDE	76	FELODIPINE
77	FENFLURAMINE HCL	78	FLUNARIZINE
79	FLUOROURACIL	80	FLUPENTHIXOL
81	FLUPHENAZINE ANATENSOL INJ	82	FLURBIPROFEN SODIUM
83	GLIBENCLAMIDE	84	GLICLAZIDE
85	GLIPIZIDE	86	GRISEOFULVIN
87	HYDROCHLOROTHIAZIDE	88	HYDROFLUMETHIAZIDE
89	HYDROXYZINE HCL	90	INDOMETHACIN
91	IODINE	92	IODOCHLOTHYDROXYQUIN
93	IOHEXOL	94	IRON SORBITOL CITRIC ACID
95	KANAMYCIN	96	KETOCONAZOLE
97	KETOROLAC TROMETHAMINE	98	KETOTIFEN

DR-13

VHAI-AIDAN-NCCDP-RDCC DRUG CONSULTATION
ON
IMPACT OF POLICY CHANGES ON DRUG POLICY AND DRUG USE
26, 27 August 1996

IRRATIONAL PARACETAMOL FDCs

Dr.W.V.Rane
Arogya Dakshata Mandal

The earliest paracetamol combination was with anti-histaminic and ephedrine as systemic nasal decongestants. Lately the Drug Controller of India has banned ephedrine anti-histaminic combinations and drug manufacturers are changing over to pseudoephedrine. British National Formulary (BNF, No.29, March 95, page 143) says "These preparations are of doubtful value but unlike the preparations for local application they do not give rise to rebound nasal congestion. They contain sympatheminetics, and should therefore be avoided in patients with hypertension, coronary heart disease, or diabetes, and in patients taking monoamine-oxidase inhibitors..... Many of the preparations also contain antihistamines which may cause drowsiness and affect ability to drive or operate machinery". I have mentioned here under the FDCs and each FDC could have many brands. For sake of convenience I have mentioned only one brand.

Paracetamol 500 mg + tripolidine 2.5 mg
+ Pseudophehedrine 60 mg.. Actified-Wellcome

Paracetamol 400 mg + Phenylephrine 5 mg
+ diphenpyraline 2.5 mg Cinaryl-Themis

Paracetamol 500 mg + Pheniramine Mal 12.5 mg Cosavil Hoecht

Paracetamol 500 mg + Phenylopropanolamine 25 mg
+ Chlorpheniramine Mal 2 mg Febrex Plus Indico

Paracetamol 500 mg + Chlorpheniramine mal 4 mg
+ pseudoephedrine 60 mg Rinostat - Searla

Paracetamol 325 mg + Dextromethorphan 10 mg + Phenylpropanolamine 25 mg + Chlorpheniramine maleate 4 mg
+ Caffeine 50 mg Alex-Lyka

Paracetamol 500 mg + Promethazine 10 mg Crophen-10 Shalaks

Paracetamol 500 mg + Codeine 10 mg + Caffeine 30 mg
+ Chlorpheniramine mal 2 mg Neofebrin-NeoPhar

Paracetamol 125 mg + Dextromethorphan 5 mg + Carbinoxamine Mal 1 mg
+ Pseudoephedrine 10 mg per 5 ml - Pedia 3 Ethnor

Paracetamol 250 mg + Analgin 250 mg + Tripolidine 1.25 mg - Recofast Ethico

Paracetamol 450 mg + Chlorpheniramine mal 2 mg + Ephedrine 5 mg
+ Bromhexin 4 mg + Glyceryl glaicolate 50 mg - Sudin Group

BNF, Physicians' Desk Reference (PDR) and Martindale Extra Pharmacopoea do not mention the combination of paracetamol and Ibuprofen. But in India it is one of the most widely promoted antipyretic and analgesic FDC. Some of the analgesic paracetamol FDCs contain opioid drugs and BNF (NO.29 March 95 page 182) says "Compound analgesic preparation containing paracetamol or aspirin with a low dose of an opioid analgesic are commonly used, but the advantages have not been substantiated. The low dose of the opioid may be enough to cause opioid side-effects (in particular, constipation) and can complicate the treatment of overdose, yet may not provide significant additional relief of pain.... In general, when assessing pain, it is necessary to weigh up carefully whether there is a need for non-opioid and an opioid analgesic to be taken simultaneously.... Caffeine is a weak stimulant that is often included, in small doses, in analgesic preparations. It does not contribute to the analgesic or anti-inflammatory effect of the preparation and may possibly aggravate the gastric irritation caused by aspirin. Moreover, in excessive dosage or on withdrawal caffeine may itself induce headache".

These are some of the Paracetamol FDCs of analgesics.

Paracetamol + Ibuprofen

500 mg + 400 mg Acetofen Mesco

333 mg + 400 mg Brucet Micro Nova

325 mg + 400 mg Anaflam Albert David

325 mg + 300 mg Brupal Geno

325 mg + 200 mg Ibugesic plus Cipla

250 mg + 200 mg Nopane Jr. Combat

162.5 mg + 100 mg Combiflam suspn/5 ml Roussel

125 mg + 100 mg Brupal Kid Geno

250 mg + 400 mg + Dextropropoxyphene 32.5 mg Bren-PX Kopran

300 mg + 400 mg + Chlormezanone 250 mg Ibuflamar MX Indico

325 mg + 400 mg + Chlorzoxazone 250 mg Brenlax Kopran

Paracetamol + Dextropropoxyphene

650 mg + 65 mg Carbutyl - Roussel

500 mg + 32.5 mg Proxytab Wockhardt

400 mg + 70 mg Dexovon U.S.V.

400 mg + 65 mg Parvon Jagsson Pal

350 mg + 32 mg Parvon-N Jagsson Pal

325 mg + 65 mg Darvocet Eli Lilly

These are types of FDC combinations and each could have hundreds of brands. There are many other FDCs as follows:

Paracetamol 500 mg + Pentazocin 15 mg Foracet Ranbaxy.

Paracetamol 300 mg + Chlorzoxazone 250 mg Dodil - Duphar

Paracetamol 450 mg + Chlormezanone 100 mg Dolobak-Brown & Burke

Paracetamol 250 mg + Mefenamic acid 500 mg Longagesic Tata Ph.

Paracetamol 500 mg + Mefanamic acid 500 mg Meftal Forte BlueCross

Paracetamol 650 mg + Ketoprofen 50 mg Redufen-A Unique

Paracetamol 500 mg + Phenylbutazone 50 mg Actimol Pharmed

Paracetamol 250 mg + Phenylbutazone 100 mg + Diazepam 2 mg
+ Magnesium, tri silicate Arcure Nulife.

Paracetamol 250 mg + Oxyphenbutazone 100 mg Uniloids
+ Dextropropoxyphene 32.5 mg Combigesic.

Paracetamol 500 mg + Oxyphenbutazone 100 mg Flamox forte Glenmark

Paracetamol 325 mg + Oxyphenbutazone 100 mg Prestigesic Synthico
+ Phenyl-iso-propylpyrazolone 150 mg

Paracetamol 250 mg + Methocarbamol 350 mg Robinaxol Khandelwal

Paracetamol 500 mg + Metoclopramide 5 mg Metopar CFL Pharma

Paracetamol 325 mg + Codeline 30 mg TWC Ethnor

Paracetamol 500 mg + Indomethacine 25 mg Idicine-P IDPL

Paracetamol 350 mg + Indomethacin 25 mg Suract SOL Ph.

Paracetamol 450 mg + Orphenadrine 35 mg Orphanol Torrent

Paracetamol 250 mg + Propyphenazone 150 mg Anafebrin Themis Chem

Paracetamol 300 mg + Propyphenazone 50 mg
+ Caffeine 50 mg Dart Juggat Pharma

Paracetamol 250 mg + Propyphenazone 150
+ Caffeine 50 mg Saridon Roache

Paracetamol 325 mg + Methocarbamol 400 mg Flexinol Protec

Paracetamol + Carisoprolol 175 mg + Caffeine 32 mg Carisoma Comp. - Wallace

Ibuprofen is not only combined with paracetamol, but there are a few more FDCs of Ibuprofen as follows:

Ibuprofen 200 mg + Pseudoephedrine 30 mg Arinac Knoll

Ibuprofen 400 mg + Pseudoephedrine 60 mg Arinac forte Knoll

Ibuprofen 400 mg + Methacarbamol 750 mg Ibugesic-M Cipla

Ibuprofen 200 mg + Metahcarbamol 750 mg Robiflam Khandelwal

Ibuprofen 400 mg + Dextropropoxyphene 65 mg Ibuproxyvon Wockhardt

Ibuprofen 200 mg + Dextropropoxyphene 32.5 mg Subdu U.S.V.

Ibuprofen 400 mg + Colchicin 0.25 mg Kebutacin-I Kee Pharma

Ibuprofen 200 mg + Chlorzoxazone 250 mg Paraflax Ethnor

This paper shows 50 different FDCs of Paracetamol with various other drugs and in different concentrations. Each type of these FDCs can have many more brands.

Ref: Drug Today June - August, '96
AIIMS, July, 1996.

DRUGS : Suggested steps / Action against drug misuse in India

DR-13

(1) 1980 : a high powered sub-committee, set up by the Drugs consultative committee (DCC - a statutory body consisting of State Drug controllers + members of the central Drug control Authority) to examine the therapeutic effectiveness of 34 categories of fixed-dose combination drugs, concluded that 23 (68%) of these categories were either irrational, therapeutically useless or outright harmful. Out of these 23 categories, 16 (or 70%) were judged by the committee to be harmful + it recommended that they should be "weeded out immediately" in the public interest. The remaining 7 were judged to have no therapeutic rationale but at the same time had no harmful potential. committee suggested their production should be discontinued gradually. In addition to these, the committee found that popular drug combinations such as penicillin with streptomycin, tetracycline + vit C, atropine + analgesic-antipyretics, + vitamins with tranquilizers were potentially harmful. The implementation of the committee's report banning these 23 drugs would endanger more than 1000 branded formulations on the Indian Market) It is not surprising that the industry swiftly denied the validity of the committees findings

List of 19 categories of fixed dose combinations that should be banned.

1. Steroids
2. Chloramphenicol
3. Ergot.
4. Vitamins + anti-inflammatory agents + tranquilisers
5. Atropine in Analgesic Antipyretics
6. Analgin
7. Yohimbine + Strychnine + testosterone + vitamins
8. Iron + strychnine, arsenic, yohimbine
9. Phenacetin
10. Tetracycline, analgin + vit C
11. Chloramphenicol + streptomycin
12. Penicillin + streptomycin
13. Ayurvedic drugs + modern drugs
14. More than one anti-histaminic
15. Penicillin + sulphonamides
16. Anti-histaminics + tranquilisers
17. Vitamins + analgesics
18. Vitamins in anti-TB drugs
19. Tranquilisers, anti-histaminics + Analgesics.

Source - 'Sunya' Indic' May 1981

A to Z of Problem Drugs

DR-13 copy

(A check-list of hazardous, banned, bannable and dumped drugs in India)

A = **Analgin** - is a potentially toxic drug and may cause agranulocytosis. Fixed dose combinations (FDC) of any other category of drug in oral dosage form are considered harmful.

Amidopyrus - was used as an analgesic, antiinflammatory agent for ~~many~~ over 70 years. ~~Now~~ It has now been found to increase the risk of agranulocytosis and in large doses, to be associated with renal tubular necrosis (Banned July 1983)

Ancoloxin - a widely used anti-nausea drug which is reported to have teratogenic potential and hence is a hazard to pregnant women. Sold in India without warning.

Anabolic Steroids: Synthetic derivatives of male sex hormone which have an androgenic and anabolic (body building) effect. It is chiefly indicated for treatment of senile and post menopausal bone disorders and aplastic anemia. In India it is advised for malnutrition, appetite stimulant, and for increasing growth. All these are foolish especially in the light of irreversible harm it can have on children's growth and sexual development. After much publicity of these side-effects CIBA Geigy has withdrawn Dianabol one of the commonest. Many more preparations continue to be marketed in India.

B = **Bromides** - On prolonged administration they replace chloride ions in the body. Cumulative poisoning manifests as conjunctivitis, gastro-intestinal symptoms, dermatitis and mental disturbances. It was a commonly used hypnotic of low potency but unreliable (Banned in July 1983)

C = **Chloral Hydrate** - used as a hypnotic has found to be an irritant of the gastric mucosa causing nausea vomiting, flatulence and epigastric distress. It can

also cause hepatic or renal damage. It should no longer be used as a hypnotic. (Banned in July 1983)

Clioquinol - or hydroxyquinolines have been popularly used for prophylaxis and treatment of gastro-enteritis, amoebiasis and travellers diarrhoea. Ever since the report of its association with SMON (Subacute myelo-optic neuropathy) its use has been restricted or banned in many countries. In India they are supposed to be prescription drugs but are obtainable over the counter. A warning in English - small print does occur on the product but it hardly succeeds in warning consumers.

D = Dipyrone is the sodium sulphonate of amidopyrines having similar properties and adverse effects. particularly fatal agranulocytosis. The incidence and risk of this hazard far outweighs any benefit that can be derived from its use.

E = EP Forte these are high dose estrogen-progesterone combinations which are dangerous for use in pregnant women because of the associated fetal malformation. Inspite of the banning of production and sales of these drugs by the drug controller in March/June 1983 these continue to be misused for hormonal pregnancy tests and for induction of abortion.

Enzymes - A very wide-range of enzymes preparations are available in India as digestives and for specific conditions. Though by themselves they are not harmful their production in large amounts along with tonics, vitamins and health restoratives are an indication of our irrational drug policy at the cost of larger social needs. These are mostly consumed by the relatively well-fed urban population.

Ergot is an alkaloid effective in the treatment of migraine. However Fixed dose combinations with drugs like paracetamol, prochlorperazine etc have no therapeutic advantage and hence are irrational. (FDC's of ergot are

banned in July 1983)

FDC's or

F= Fixed Drug Combinations - These are formulations where two or more drugs are combined for the following reasons a) synergistic action b) corrective action c) two or more drugs normally prescribed together and taken by patient simultaneously d) when dosage of each drug need not be individualised e) where combination ensure better patient compliance due to convenience of administration. Conversely FDC's are irrational and should not be permitted if a) adverse interactions occur b) when one of the combined drugs becomes toxic on prolonged use c) when abrupt withdrawal of one causes withdrawal symptoms d) If sub-therapeutic doses are used in the absence of clinically demonstrable synergism e) when pharmacokinetic behaviour of individual agents is different.
(22 FDC's were banned in July 1983 - refer Government order.)

G= Gripe Water - These are popular preparations promoted for colic in children. Contain alcohol and sodium bicarbonate. Chronic use of the latter can cause milk-alkali syndrome. Uncomfortable but rarely dangerous gastric distension can also occur. Despite toxicity and side effects gripe water does a thriving business through medical and consumer ignorance. (Banned in Bangladesh in June 1982)

H = Hydroxyquinolines or halogenated oxyquinoline derivatives which include iodochlor-hydroxy quinoline, proxyquinoline, halquinol, diiodohydroxy quinoline, chlorquinaldol, chiniofon.)
For hazard see Clioquinol.

Hormonal Pregnancy Tests - ~~Mixture of~~ Oestrogen-progesterone combinations have been indiscriminately used in pregnant women as a hormonal test to detect pregnancy. (See E P Forke) Since there is an increased risk of foetal abnormalities and the test is false

positive in one out of five women these tests should no longer be done. Drugs controller had issued a directive to strengthen warning on packages (March 1982) and banned manufacture (Dec 1982) and sale (June 1983). Due to legal controversy, and professional and consumer ignorance it still continues to be used.

I = Injections - have played a very important role in the modern medicine and form one of its most distinctive features. However it has also lent itself to a very large degree of misuse - overuse because of the mystique associated with it in the minds of the public and the temptation of the medical practitioners to pander to this need and pressure for their own economic gain

J = 'Junk' Drugs - These are newer formulations in the market whose only additional values are cosmetic embellishments, added flavours, elegant packing, irrational combinations - all of which help to increase its cost.

K = Kaolin - is a hydrated and purified aluminium silicate a common addition in antidiarrhoeal mixtures. Along with pectin and bismuth salts it forms a group called adsorbents, astringents and binding agents. These drugs may cause loss of electrolytes by preventing absorption through gastrointestinal tracts. If at all, they are of cosmetic value and may actually mask the severity of disease.

L = Lomotil or diphenoxylate and Loperamide are drugs whose risks of treatment outweigh their benefits especially in children. They are commonly used in diarrhoeas and the dangers of paralytic ileus leading to inaccurate assessment of fluid loss and toxaemia if associated with gut infections make them especially dangerous in pediatric practice. Their use for children under 6 has been banned in India. In most other countries its use is banned altogether.

M = Mepyrilene and its salts

Banned in July 1983

N= Nialamide (or Niamid) - a MAO inhibitor used in the treatment of depressive disorders. (Banned in Turkey 1983)

O= OTC drugs or over the counter drugs
These are drugs that are available to consumers without prescription and are mainly painkillers, anti-cold, anti-cough preparations, cough mixtures, tonics, food substitutes and protein powders. Many of them are costly compared to the benefits they render, have some ingredients which are unnecessary or useless but helping to push up cost and are widely advertised with false claims to push up sales. There is a need for scientific scrutiny as also a systematic campaign against their irrational ingredients or claims.

Oxyphenbutazone - These are a group of non-steroidal anti-inflammatory drugs which also have mild anti-pyretic and analgesic properties. The dangers associated with use are bone marrow toxicity and liver toxicity. They are widely used/overused/misused group of drugs and there is great need for building professional awareness and consumer alert on this group of drugs. Recently these drugs have been banned in the U.K.

P= Phenacetin - was a commonly used analgesic/anti-pyretic agent which has been reported to cause kidney damage and failure and hemolytic anemia. Hence fixed dose combinations containing it are now considered outdated and ~~useless~~ hazardous. These have been recommended for weeding out by the Hathi Committee.

Phenylbutazones - another group of non-steroidal anti-inflammatory drugs which give only symptomatic relief and in no way alter the course of the illness. Its main indications are for ankylosing spondylitis and rheumatoid and gouty arthritis. Though they are being widely promoted and used for non-rheumatic disorders and aches, pains and fever. Bone marrow toxicity is a real danger with the use of this drug

and hence its use should be severely restricted. Its present availability - freely over the counter and should be drastically controlled and its deadly combinations with aminopyrin, analgin, paracetamol, diazepam, Vitamin B, dextropropoxyphene acetaminophen should be banned or adequate warnings in labels instituted

Practolol = (Banned in July 1983)

Penicillin - still an important constituent of antibacterial therapy in spite of the risk of anaphylactic reaction and allergic reactions (Its combination with sulphonamides and its preparations as skin/eye ointments are banned from July 1983)

Q = Quinine - was the sheet anchor of antimalarial treatment till safer 4 aminoquinolines and 8 aminoquinolines were developed Its use leads to blackwater fever so is restricted nowadays for treatment of chloroquin resistant cases or sometimes in cerebral malaria

R = Rational drug therapy - is the art/science of prescribing the best suited drugs to individuals who need them taking and not to those who merely want them. It's takes into account factors like efficacy, safety (low incidence of side effects), cost and ease of administration It scrupulously avoids extragarant prescribing, over or under prescribing, multiple prescribing or incorrect prescribing.

S = Sulphonamides - These have an important role to play in the therapy of infections. The combination with penicillins is undesirable because of the antagonism of antibacterial effect when bacteriostatic and bacteriocidal drugs are given together. (FDCs of sulphonamides and penicillins are banned since July 1983)

Streptomycin

Since it is one of the most effective drugs in anti-TB treatment its use should be limited to TB treatment and mixed infections of the gut. Its combination with penicillins is undesirable since its use in small doses promotes development of resistance.

Steroids - one of the most misused drugs in general practice because of acute onset of beneficial

effects. Patients are exposed to a wide range of toxic and adrenal insufficiency due to adrenal suppression cumulative effects. Its a life saving drug to be used in special circumstances. Their doses should be adjusted to the minimum that can produce the effects. Fixed dose combinations with other drugs are therefore irrational and objectionable since this individualization of the dose cannot be done. (FDCs of steroid for internal use except for treatment of asthma are banned since July 1983)

Strychnine - This was a drug formerly used as an appetiser. Its use in tonics can induce convulsions particularly in susceptible individuals An obsolete drug! (FDCs of strychnine with caffeine, yohimbine, testosterone and vitamins are banned since July 1983)

T= Tetracyclines - one of the most commonly misused/overused broad spectrum antibiotic mistakenly thought to be free of dangers. Reports of its ability to cause discolouration of teeth, catabolic effect on protein synthesis, diarrhoea, increased intra-cranial pressure in children, Fanconi syndrome (if outdated, degraded drug is used), liver damage in pregnant women make have put it in the list of hazardous drugs. It should not be used in Paediatric practice especially as a syrup and in pregnant mothers. Its manufacture is proposed to be banned from January 1982.

T= Tonics. Apart from being an economic waste, most tonics in the market contain alcohol which is the main appetite stimulant and also vitamin and mineral constituents in amounts greater than the physiological absorptive capacities of average GI Tracts. Their overuse thus mainly help to vitaminise our sewage systems!

U= Unani and Ayurvedic drugs - These are difficult to standardise since official standardisation methods are not available. FDC's of these with allopathic drugs have no therapeutic rationale or justification or proven efficacy. (FDC's of ayurvedic and unani drugs with

modern drugs have been banned since July 1983)

V= Vitamins - a typically misused/overused group of agents especially as combinations and tonics. They are essential nutritional requirements but most people get adequate amounts in a balanced diet. Their specific and separate preparations are required for specific deficiency states or as adjuncts to therapy. Their FDC's with analgesics, tetracyclines, anti-inflammatory drugs, tranquillisers have no proven therapeutic effects and have been banned since July 1983)

W= Wolfenbuegs is one of the brand leaders in the tonic market whose main effects if any are because of the 9-16% alcohol content. It contains insufficient amounts of iron, and creosotes and guaicols whose role in man has not been definitively established. Like Incremin, Phosphonic, Hemipos their advertised claims far surpass their actual chemical content. Advertisments of such tonics are the most symbolic of high-pressure, half truths gimmicry of medical advertising.

X=

Y= Yohimbine - a drug often combined with strychnine, vitamines, testosterone, arsenic, iron and vitamins has been found to penetrate the CNS and cause central excitation including rise of blood pressure, heart rate, hyperexcitability, and tremor (Its use especially in such combinations is banned since July 1983)

Z=

Furthur Reading

1. Banned Brand Drug List
2. Hazardous Banned Bannable and Dumped Drugs
3. Rationality in Banning Fixed Dose Combinations
4. Some painful Facts about a painkiller called Amidopyrine
5. Why not to prescribe Anabolic steroids.?
6. Irrational use of antibiotics
7. The Clioquinol Controversy
8. Using Tetracyclines For Children and pregnant women
9. Consumer Alert - Phenylbutazone and Oxyphenbutazone
10. Scientific scrutiny of some over the counter drugs
11. The case against E P For Ve Pregnancy tests safe?
12. National Drug policy guidelines and list of banned drugs (Bangladesh)

Available From Low cost Drugs & Rational Therapeutic Cell, Voluntary Health Association of India, C-14 Community Centre, SDA, New Delhi -110016.

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The E P Case

Mira Shiva

High dose combination of Oestrogen and Progesterone has finally been banned. It is tragic that the public had to fight for 6 long years for getting a hazardous drug combination banned, that too against all odds.

It was the socially conscious health activists and consumers bodies that had initially raised the issue in the first place, when the EP campaign was launched way back in 1982 on Women's Day on 8th March. Due credit goes to the press for keeping the issue alive all these years and supporting the stand of the people.

It was the drug health and consumer groups who protested when on 21st July 1982, the ban order for manufacture was given as December 1982 and ban for sales as June 1983. How could a drug recognized as hazardous be allowed to be manufactured and then sold for almost another one year ? It was not surprising when this was misused by the manufacturers to challenge the hazardous nature of the drug, saying that if the drug was hazardous wouldn't it have been banned immediately by the DC authorities and since it wasn't – it was obviously non hazardous !

The Legal Battle

The drug companies were quick enough to find the legal loopholes and the stay order against the ban order *was* obtained from the Calcutta and Bombay High Courts on legal technicalities. The fact that it involved a hazardous drug which could maim and cripple the unborn foetus when consumed by ignorant pregnant women, –did not appear to be a matter worth considering. Even making an attempt to find out the number of women put at risk, with annual sales of Rs. 7 crore worth of drugs (majority of them are consumed for pregnancy tests and for induction of abortion though on paper the indications permitted had been only for secondary amenoorrhea) was not done.

Questions were raised in the Parliament, repeated requests were made to the Health Ministry and Chemical Ministry to make attempts at getting the stay vacated.

In the words of Supreme Court Justice probably the government never wished to vacate the stay; this became obvious because the subsequent events are pointers to scheming.

Again it was due to a writ petition that Supreme Court took up the issue again. Justice Ranganath Mishra's comments on banning of drugs is a telling commentry .

> "This court as early as 11.4.1983 directed issue of notice to the Medical Council of India, The Indian Medical Association, The Drugs Medical Council of India, The Indian Medical Association & The Drugs Control Authorities of the States except that of Kerala, as it was already made a respondent to the writ petition. Obviously such notice was given as in the opinion of the Court, the matter was one of great importance and the Court looked for participation of these authorities in the debate with a view to assisting the Court in the disposal of the matter. We are surprised that the notice from the Court has not evoked response excepting the State of Karnataka. Statutory bodies when called upon by a Court, in particular the apex Court of the Country, are duty-bound to respond and join the proceedings before the Court. These bodies are not litigants and do not have the choice of keeping away from the Court like private parties in ordinary litigations opting to go ex–parte. The present matter is certainly one which is sufficiently important and the stake of the entire nation is high; when the Court *suo moto* extended the opportunity of being heard and invited the named statutory or other authorities to come forward and place their view

points on relevant aspects, an attitude of callous indifference cannot be appreciated. We hope and trust that there would be no repetition of such a situation".

The Public Hearings

It was unfortunate for public that the public litigation case was referred back to the Drug Controller of India. In its Court Order of November 1986 Supreme Court gave direction to hold public hearings to seek the views of consumers and health groups and decision be taken by end of July 1987. The drug companies were shrewed enough to use the professional bodies like FOGSI (Federation of Obstetrics Gynaecology Society of India) to be their spokesman. FOGSI till the very end continued to support the stand of the Drug manufacturers stating that the drug was essential and absolutely safe. Luminaries such as Dr. C. L. Jhaveri, Dr. C. S. Dawn, Dr. B. N. Purandare did their utmost to tilt the balance in favour of the manufacturers. The role of the WHO expert and the Deputy Drug Controller who chaired the Calcutta hearing was not very creditable.

The silence of professional and academic bodies such as IMA, IMC, at such a time was unforgivable. It was only the Indian Academy of Paediatrics that had expressed its deep concern against the continued sales of high dose E. P. drugs. The public hearing in Bombay ably proved that when called upon, the women's organisations can give a bitter fight for a cause. Even the public notices for the public hearings were inserted inconspiciously in the papers, the hearings were stated to be for "formulations of oestrogens and progesterone", in the first public notice and "combination of oestrogen and progesterone" for the second one. The failure to clearly state that the public hearings were being held to decide whether or not to ban combination of high dose Estrogen-Progesterone, was too significant to be overlooked as an unintended-errors. The way the 4 public hearings in Madras, Delhi, Calcutta and Bombay were held on 5th Feb., 10th April, 10th July and 14th July 1987 respectively is a story in itself. Even when the Drug Technical Advisory Board met in May 1988, the minutes of the 4 public hearings were not made available, nor the summary of the arguments for and against the drug ban was sent to Boards members for prior information. The fact that it took 6 long years to issue a Gazette Notification to ban a drug – shows the forces working on it. A drug, which is known to be hazardous – which has been mainly used in pregnancy – a drug which was banned by the Drug Controller of India himself in 1982 – a drug which ICMR strongly recommended to be banned in 1982 as well as in 1987 – a drug which was not allowed to be registered or sold in the parent country Netherlands by Organon Infar, was strongly contested by drug manufacturers and they had the audacity to challenge the DCI's ban order in India.

Enforce the ban immediately

The EP case involved a drug which the contemporary Gynaecological medical literature does not even mention, as it has no role–and as it is not used by any gynaecologist or a doctor, as safer alternatives exist. Not merely had several drug regulatory authorities banned the drug, but several companies had withdrawn the product themselves. It was due to sheer gist and perseverance of the drug activists, health and consumer groups that the ban order has come now. Should this be counted as success ?

We have learnt from past experience that unenforced drug bans are as bad as no bans. The Gazette Notification was issued on 15th July 1988. Government media of AIR and Doordarshan should have been used to inform the chemists, medical professionals and the ignorant consumers about the drug clearly stating the brands and their manufacturers ! The Drug Control Authorities owe this to the nation. The stocks from the manufacturers and the market should be withdrawn and destroyed.

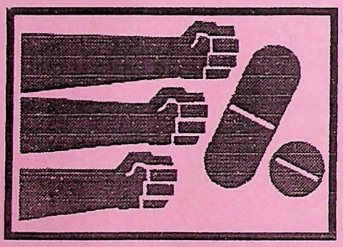
The Health Ministry has had 6 long years to make available to the medical professionals the recommended alternatives. Safe, low cost simple pregnancy tests, which basic health workers can use, should be easily available as part of Mother and Child Health Programme. Permitting at this stage the manufacturer and sales of high dose EP drugs as single ingredients in the same dose would be ridiculing and sabotaging the ban. The ban has come 6 years too late; now the implementation of the ban must be immediate. The Drug Control Authorities and the manufacturers must be held responsible if these drugs continue to be sold. If this could happen for a drug like high dose EP which the consumers and health groups considered a watertight case–what would be the fate of other many hazardous drugs ? Let the government and Drug Controller of India announce how they are going to make the ban effective. ▣ ▣

DR-13.

STUDY OF PAIN KILLERS

(ANALGESICS & ANTIPYRETICS AND NSAIDS)

LISTED IN A COMMERCIAL PUBLICATION FOR DOCTOR'S USE



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STUDY OF PAIN KILLERS (ANALGESICS & ANTIPYRETICS AND NSAIDS) LISTED IN A COMMERCIAL PUBLICATION FOR DOCTOR'S USE.

Pain killers are a group of drugs that are most commonly used. This study is an attempt to bring to the notice of the consumers regarding the type of pain killers that are available for : doctor to prescribe to the patient. Are the drugs promoted to doctors' from the list of Essential Drugs by WHO? Are the drugs scientific? And if the pricing of drugs is justified.

WHY THIS STUDY?

Pain is perhaps the most common symptom for which patients seek guidance and help from doctors. Pain killers are a group of drugs that are extensively used both by general practitioners and consultants.

Drug Action Forum - Karnataka (an independent, non-profit and non – governmental organization campaigning for Rational drugs and policies) took up this study, with an attempt to bring to the notice of the consumer, regarding the type of the pain killers that are commonly promoted to doctors. A commercial publication used exclusively by doctors was referred to get the common pain killers that are promoted by various drug manufacturers.

The study is mainly aimed for consumer groups that are actively involved in building awareness among consumers by involving in campaigning and lobbying for rational drugs. It is hoped that the consumer groups would be better equipped to lobby for rational drugs, when dealing with drug policy makers, with studies of such nature.

The study is relevant because in India, doctors after passing out from the medical colleges have no access to unbiased and scientific information to them regarding drugs. They are often compelled to depend upon the information that is given to them by drug companies or at times by information that is supplied to them through company sponsored seminars. Often drug companies promote irrational drugs to doctors. Using the case study of pain killers, this study confirms the above statements.

Industry promotion – in the form of direct-mail brochures, journal, displays, professional courtesies or detail person or pharmaceutical representatives – is intended to be persuasive rather than educational.
The pharmaceutical industry cannot, should not, and indeed does not purport to be responsible for the education of physicians in the use of drugs.
Goodman & Gilman's. The Pharmaceutical basis of therapeutics. 10th edition. Page number 64

The study is mainly under two heads:

i. Rationality: - Does the drug listed in the commercial publication (MIMS), match with the Essential Drug list by WHO? And is the drug rational?
ii. The drug prices. - Comparing the Essential Drug prices set by different companies.

(I) Is the drug Essential and Rational?

For the sake of this study three publications have been used. One is a commercial publication used by doctors extensively all over India and the other two are scientific publications. Among the scientific publications one is the well known "WHO model list of Essential Drugs", first published in 1977 and has been regularly updated every two years. The other scientific publication is "The Pharmacological Basis of Therapeutics", 10th edition by Goodman & Gilman, a standard text book which is used for reference and study by academic medical professionals all over the globe.

a) Monthly Index of Medical Specialities (MIMS) :-

The commercial publication is "Monthly Index of Medical Specialities" known popularly by its acronym MIMS (www.mims-india.com). The June 2004, volume 24, number 6 issue of MIMS lists in its index, 90 groups of drugs under different categories. But for the present study only two categories were selected. Firstly Analgesics & antipyretics and secondly NSAIDs. (Analgesics is a term used for all categories of pain killers. Antipyretics are drugs that reduce fever. NSAIDs is an acronym for Non Steroidal Anti-Inflammatory Drugs, a term used for all categories of drugs that reduce inflammation and do not belong to the steroid group of drugs). All these analgesics & antipyretics and NSAIDs are available in various forms (like tablets and syrups etc) and also different dosage forms. Totally 235 formulations (manufactured by 49 drug companies and sold under 120 brands) were systematically scrutinised with reference to World Health Organization (WHO) Model List and a standard text book of Pharmacology.

b) WHO Model List of Essential Drugs :-

The WHO Model list of Essential Drugs 2003 referred to in this study contains about 375 drugs in 500 formulations (or dosage forms). These could provide safe, effective treatment for the vast majority of communicable and non-communicable diseases. Essential Drugs should be the drugs of first choice, more so in a situation where financial resources are a crunch. The list was first published in 1977 by WHO and has proven that most diseases can be managed with few medicines. All the 235 drugs in our study were checked to see whether they are included as Essential Drug or not.

OF THE TOTAL 235 FORMULATIONS LISTED FOR THIS STUDY ONLY 23 (9%) MATCHED WITH ESSENTIAL DRUGS.

Rationality :-

To assess whether the drug is rational or not, a standard text book of Pharmacology, titled Goodman & Gilman's "The Pharmacological basis of Therapeutics" was referred. This is a standard text book, used extensively by teachers and medical students during medical teaching and training.

The term "rational" is used for drugs that are scientific in nature by being referred and recommended or mentioned in standard text books. Irrational drugs on the other hand do not find mention or are not recommended in such text books. So with the help of the text book the following two criteria were evolved:-

1. Firstly if the formulation is not mentioned in the book (for example combination like Paracetamol with Ibuprofen) then it is considered as irrational
2. Secondly if the formulation is described but the text book does not advocate it, the formulation is considered as irrational (for example Analgin or Nimesulide).

If a certain formulation does not fall under both the above mentioned criteria, it is labeled as Rational drug

What is Rational drug?
If their efficacy is clinically proven and the therapeutic benefits outweigh the risks, they are called as rational drugs

What is irrational drug?
If there is no good clinical pharmacological evidence on their therapeutic benefit and safety then, such drugs are considered as irrational drugs.

The presence of irrational drugs is not only an economic burden but also can be harmful. This is truer for developing country like India.

OF THE TOTAL 235 FORMULATIONS THAT WERE STUDIED A TOTAL OF 95 (40%). THUS THE NUMBER OF RATIONAL DRUGS ARE 140 (60%).

SUMMARY OF THE STUDY (part 1)

Of the total 235 formulations that were screened only 22 (9%) confirmed to the Essential Drug list of WHO, 140 were (60%) rational drugs and remaining 95 (40%) were irrational.

Only one out of every ten drugs that are promoted to doctors confirm to WHO's Essential Drugs. And out of every ten drugs, six drugs are rational. From this it is obvious that if a doctor prescribes a drug, there is only one in ten chances of prescribing the drug of first choice. This is not an acceptable situation where financial resources are always a major crunch.

Some interesting observations:- Following were some of the interesting observations after the study.

1. A reputed (?) multinational company (Aventis) manufactures and sells the drug Analgin. This drug is absolute as several safer alternatives exist.

2. Another hazardous (harmful) drug is Nimesulide. It is manufactured by 5 companies, and amongst them 4 companies manufacture the drug for use in children too. This drug has never been allowed in USA and banned in several European countries.
3. Diclofenac – a pain killer often used by both specialists and general practitioners is also manufactured in the form of injectable. The injectable form of this drug is not mentioned in the standard text book (The Pharmacological Basis of Therapeutics, 10th edition by Goodman & Gilman), that has been referred for this study.
4. Aspirin – a popular and most commonly needed pain killer is not manufactured by any drug company. Aspirin is listed in WHO's list of Essential Drugs. Only one drug company i.e. Nicholas Piramol manufactures an irrational combination of Aspirin (Acetyl Salicylic acid) 350 mg with Caffeine 20 mg under the trade name Micropyrin. So this study observes that some drugs which are on the WHO's Essential Drugs list are not promoted to the doctors by any drug company. In fact Aspirin should have been made available for the doctors' to prescribe.
5. A combination of the drug Ibuprofen with Paracetamol is perhaps the most widely used irrational combination. In this study 6 drug companies manufacture this drug and most of them even have the preparation for use in children (in the form of syrup). A question often raised by the consumer is that, why do doctors prescribe such an irrational combinations. As mentioned above one factor is that such drugs are heavily promoted by the drug companies to the doctors. During medical education students are taught by the teachers that such combinations are irrational and that they can be harmful to the patients, but as they start prescribing drugs to patient, the flood of misinformation by companies overshadows the scientific information.

(II) Cost analysis of Essential Drugs

The second part of the study analyses the cost of the Essential Drugs listed in MIMS. This part of the study is important as it gives a picture to the consumer regarding the cost of the drugs that should have been of top priority for a doctor to prescribe.

WHO's Essential Drugs list has only three NSAIDs viz. Paracetamol, Ibuprofen and Aspirin. As Aspirin is not manufactured by any drug company we studied the pricing of only two drugs i.e. Paracetamol and Ibuprofen.

Following are the highlights:-

a. Paracetamol 500 mg is manufactured by 6 drug companies. Amongst them 2 drug companies (SKF and Nicholas Piramol, the former being a multinational) manufacture and sell the same drug Paracetamol under two different brand names with different pricing. There can be no scientific justification for this.

(For details refer to the chart on next page).

Chart showing the drug Paracetamol being sold by different companies with varying cost

Sn	Trade name	Generic name	Price of the drug for 10 tablets.	Manufacturer
1	Calpol	Paracetamol 500 mg	Rs. 8.78 / 10 Tablets	GSK
2	Crocin	Paracetamol 500 mg	Rs. 7.98 / 10 Tablets	
3	Disprin Paracetamol	Paracetamol 500 mg	Rs. 9.40 / 10 Tablets	Reckitts
4	Doliprane	Paracetamol 500 mg	Rs. 4.88 / 10 Tablets	Nicholas Piramol
5	Molidens	Paracetamol 500 mg	Rs. 4.21 / 10 Tablets	
6	Pacimol	Paracetamol 500 mg	Rs. 6.30 / 10 Tablets	IPCA
7	Ultragin	Paracetamol 500 mg	Rs. 8.80 / 10 Tablets	Wyeth
8	Pyrigesic	Paracetamol 500 mg	Rs. 13.50 /10 Tablets	East India

b. The lowest priced Paracetamol is for Rs 4.21 and the costliest is at Rs 13.50. A whooping price difference of 69%. How does one explain such a huge price difference? Drug companies spend lot of money in promoting a drug to the doctor and this cost is recovered by hiking the price of the drug. Doctors are neither taught during their student days nor do the drug companies mention its price (cost) when they promote the drug to doctors. So doctors tend to prescribe the costliest. Unfortunately the consumer also believes that a costly drug is better acting. The consumer is not aware that one could buy the same drug of another company at a much lower rate. Medicines are the only commodities in the market where the buyer is not the chooser.

Drug pricing of Ibuprofen 400 mg did not show much variation.

sn	Trade name	Generic name	Price of the drug for 10 tablets	Manufacturer
1	Brufen	Ibuprofen 400 mg	Rs. 5.05 10 Tablets.	Knoll
2	Ibugesic	Ibuprofen 400 mg	Rs. 5.93 10 Tablets.	Cipla

Drug pricing of Diclofenac 50 mg: - Diclofenac is another common pain killer used though not in the list of Essential Drugs by WHO. This drug has wide variation in prices from one drug company to another, as shown in the chart below.

sn	Trade name	Generic name	Price of the drug for 10 tablets	Manufacturer
1	Voveran	Diclofenac 50mg	Rs 15 / 10 Tablets.	Novartis
2	Tromagesic	Diclofenac 50 mg	Rs. 3.15 / 10 Tablets	Themis Chemicals

SUMMARY OF THE STUDY (PART II)

Drug prices need to be regulated by governments. But this study shows that Essential Drug prices show such wide variation. This is an area that needs further studies. But suffice it to say that drug pricing is not properly regulated by the government. There is an urgent need for consumer groups to be actively involved in bringing awareness on this issue.