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WORLD HEALTH ORGANIZATION

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No. 166

EFFECT OF RADIATION ON HUMAN HEREDITY:

INVESTIGATIONS OF AREAS OF HIGH NATURAL RADIATION

First Report of the Expert Committee on Radiation

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization.

WORLD HEALTH ORGANIZATION

GENEVA

1959

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EXPERT COMMITTEE ON RADIATION

Geneva, 28 July - 2 August 1958

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EFFECT OF RADIATION ON HUMAN HEREDITY: INVESTIGATIONS OF AREAS OF HIGH NATURAL RADIATION

First Report * of the Expert Committee on Radiation

INTRODUCTION

The first meeting of the WHO Expert Committee on Radiation (Effects of Radiation on Human Heredity) was held in Geneva from 28 July to 2 August 1958. Dr M. G. Candau, Director-General, opened the meeting and welcomed the participants. Professor J. V. Neel was elected Chairman, Professeur A. Franceschetti, Vice-Chairman, and Dr W. J. Schull, Rapporteur.

1. The General Problem

With the increasing use of ionizing radiation in medicine, science and industry, there has been concern in many quarters about the genetic effects which might be produced in man. From a public health point of view, modern discoveries concerning radiation hazards are disquieting, but it is difficult to set limits to, say, the medical use of radiation, or to determine the risks of radioactive waste discharged into the environment, until a clearer, quantitative conception emerges of the degree of genetic or somatic harm that might result. The need for further information was pointedly stated by the WHO Study Group on the Effect of Radiation on Human

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* The Executive Board, at its twenty-third session, adopted the following resolution :
The Executive Board

1. NOTES the first report of the Expert Committee on Radiation (Effect of Radiation on Human Heredity);
2. THANKS the members of the Committee for their work;
3. EMPHASIZES the extreme importance of this type of study, and expresses the desire that the Organization give all possible assistance in furthering such investigations;
4. THANKS the Government of India for its help in the studies carried out preliminary to the work of the Committee; and
5. AUTHORIZES publication of the report.

(Resolution EB23.R15, *Off. Rec. Wld Hlth Org.*, 1958, **91**, 13)

Heredity [1] as follows: " Only in the light of more knowledge can decisions be taken to define more accurately the maximum amount of exposure which may be accepted by individuals and populations without risk of serious harm." The Study Group recognized that the opportunities for expanding our information on radiation-induced mutations and their fate through studies on human populations are few in number. One untapped source of information suggested was the study of populations exposed to relatively large amounts of background radiation, that is, radiation of the order of one rem per year.

There is no doubt that those concerned with radiation protection are desirous of seeing an effort made to exploit the information potentially available in the high-radiation areas if it is feasible to do so. It is patent, however, that great difficulties are involved in designing and implementing relevant studies. Furthermore, since it seems unlikely that any one area of high natural radiation can provide sufficient data to permit firm conclusions to be reached concerning the risks to human populations of sustained exposure to low levels of radiation, it is clearly desirable that, in so far as possible, studies on these special populations be conducted with a view toward the ultimate synthesis of observations from several areas. This and other considerations require the specification of certain principles for the planning of investigations of high radiation areas. It is the purpose of this report to consider the general principles of planning investigations of high radiation areas which might apply to any part of the world; and to illustrate the application of these principles to a specific situation, namely, in parts of Kerala State, and adjoining areas of Madras State, India. The reasons for this choice will be apparent later.

2. Survey of Known Areas of High Background Radiation

A certain amount of information on natural levels of radiation in the world is contained in the report of the United Nations Scientific Committee on the Effects of Atomic Radiation.[2] For the convenience of the reader, and preparatory to a consideration of the feasibility of investigating the areas of high-background radiation, certain tables are reproduced from this and other pertinent documents.

Cosmic ray intensities (ionization in ion-pairs/cm^3 sec) and the corresponding dose rates in air at NTP are given in Table 1 for certain locations. The table shows that an increase in altitude from 0 m to 3000 m gives

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[1] World Health Organization (1957) *Effect of radiation on human heredity*, Geneva, p. 11

[2] United Nations, Scientific Committee on the Effects of Atomic Radiation (1958) *Report* ..., Annex B: *Radiation from natural sources*, New York, p. 49 (document A/3838)

TABLE 1. COSMIC RAY INTENSITIES AND DOSE RATES

Altitude (metres)	Intensity (ion-pairs/cm³ sec)		Dose rate (mrad/year)	
	At 50° latitude	Near equator	At 50° latitude	Near equator
0	2.8	2.4	41	35
1 500	4.5	3.0	66	44
3 050	8.8	6.1	128	89
4 580	18	12	263	175
6 100	34	23	500	340

an approximately three-fold increase in intensity, while the latitude variation even at 3000 m is only 50%. Neher's data for sea-level intensity, on which Table 1 is based, are 30% higher than those of other observers. Therefore, the values given in this table may be considered as upper limits.

Other data relating to natural sources of radiation are shown in Tables 2 and 3.

TABLE 2. DOSE RATES OF EXTERNAL GAMMA IRRADIATION FROM THE ELEMENTS Ra, U, Th AND K CONTAINED IN TYPICAL ROCKS OF VARIOUS ORIGINS

Type of rock	Dose rate in mrad/year * from			
	^{226}Ra	^{238}U	^{232}Th	^{40}K
Igneous rocks	24	25.8	36.8	34.6
Sedimentary rocks :				
Sandstones	13	7.7	18.4	14.6
Shales	20	7.7	30.6	36
Limestones	7.7	8.4	4	3.6

* Calculated from equations (1) and the data in Table VI of the report of the United Nations Scientific Committee on the Effects of Atomic Radiation (see footnote on p. 4).

A factor which has to be taken into account in preparing figures such as those in Table 3 is the shielding effect of the body tissues external to the gonads. The values for this factor shown in Table 4 were calculated by Spiers and are taken from a report by the Medical Research Council of Great Britain.[1]

[1] Great Britain, Medical Research Council (1956) *The hazards to man of nuclear and allied radiations*, London

TABLE 3. DOSES OF EXTERNAL AND INTERNAL IRRADIATION FROM NATURAL SOURCES UNDER USUAL CONDITIONS AT SEA LEVEL

Irradiation	Dose (mrem/year)
	To gonads and other soft tissues *
External irradiation:	
Cosmic rays	28
Gamma rays out-of-doors	47
Internal irradiation:	
^{40}K	19
^{14}C	1.6
^{226}Ra	?
Total irradiation from all sources	95

* Including bone marrow, the contribution from radium in bone being only about 0.5 mrem per year.

TABLE 4. GONADAL SHIELDING FACTOR FOR GAMMA RAYS IN THE HORIZONTAL, SITTING AND STANDING POSITIONS

Position	Shielding factor			
	Female	Average	Male	Average
Horizontal	0.52		0.67	
Sitting	0.58	0.56	0.70	0.70
Standing	0.59		0.72	
Mean factor for both sexes : 0.63				

TABLE 5. MEAN DOSE OF IRRADIATION TO GONADS AND BONES FROM NATURAL EXTERNAL SOURCES IN NORMAL AND MORE ACTIVE REGIONS

Region	Population in millions	Aggregate mean dose* (mrem/year)
1. Normal regions	2 500	75
2. Granitic regions in France	7	190
3. Monazite region, Kerala in India	0.1	830
4. Monazite region, Brazil	0.05	315

* Using a shielding factor of 0.63 for γ-rays and a dose rate of 28 mrem/year due to cosmic rays.

Taking these factors into account, the figures given in Table 5 have been advanced for different regions.

Inspection of Table 6 will afford an idea of the extent to which some of the high-radiation areas now known differ with respect to the variables which determine the feasibility of, and the weight to be attached to, an investigation of a given radiation area. Not immediately evident from this table are the difficulties within any given area of mounting and maintaining a study of the scope necessary to detect the small differences which there is reason to expect. It is not the purpose of this Committee to present in detail the special problems posed by each of the areas given in Table 6; it should be pointed out, however, that on the face of the data given in this table the Kerala area of India would appear to be the only area now known which might profitably be investigated. Although there are other areas with larger populations, the levels of radiation obtaining there are such that it is extremely doubtful whether an investigation would yield significant data bearing on the radiation problem. At this juncture, it might be well to state that the Committee is under no illusions regarding the probability of any investigation of high background areas leading

TABLE 6. SOME PARTICULARS OF AREAS OF HIGH NATURAL RADIATION

A. Areas with increased radioactivity from soil or rock

Area	Population	Demographic information available	Natural radiation received (multiply by 0.63 to get gonad dose)	Possible control populations
Part of Kerala State and adjoining area in Madras State	Approx. 80 000	Some information on births and deaths: could probably be developed relatively easily	Approx. 1300 milliroentgen per annum (plus about 200 mrad beta rays)	Similar ethnic group further along coast
Monazite area in Brazil (States of Espirito Santo and Rio de Janeiro)	Approx. 50 000	Specially prepared statistics would be required	Average 500 mrad/year	?
Mineralized volcanic intrusives in Brazil (States of Minas Geraes and Goiaz) — 6 km² in a dozen scattered places	Pastureland, scattered farms, 1 village with 350 inhabitants	Very little	Average 1600 mrad/year Peak value 12 000 mrad/year	?
Primitive granitic, schistous and sandstone areas of France with slight elevation of natural radiation said to cover about 1/6th of French population (7 million)		Specially prepared statistics would be required	180-350 mrem/year	Remainder of France estimated at 45-90 mrem/year

There are also some areas of high natural radiation in the Belgian Congo, but these are said to be uninhabited.

TABLE 6 *(continued)*

B. Areas with high natural radiation in houses made of special materials

Area	Population	Demographic information available	Natural radiation received (multiply by 0.63 to get gonad dose)	Possible control populations
Sweden — houses made of light-weight concrete containing alum shale	Relatively small	Special statistics being obtained	158-202 mrad/year (cosmic radiation excluded)	Wooden houses 48-75 mrad/year (cosmic radiation excluded)
United Kingdom (Aberdeen) — houses and buildings made of granite	Population of Aberdeen approx. 186 000	Leukaemia statistics being studied	Results from a few buildings indicate 102 mrad/year	Approx. 78 mrad/year in other cities with brick buildings, e.g., Dundee — population 178 000
Austria — granite houses	?	Special statistics necessary	Granite houses 85-128 mrad/year Brick or concrete houses 75-86 mrad/year	Wooden houses 54-64 mrad/year

C. High-altitude areas *

Area	Population	Demographic information available	Natural radiation received (multiply by 0.63 to get gonad dose)	Possible control populations
La Paz, Bolivia (altitude about 11 909 ft (3630 m); latitude 16°S)	Approx. 319 600	Some statistics available but not comprehensive	Approx. 3-fold increase in cosmic rays near equator at 3000-4000 m above sea level. Cosmic radiation tends to be about a third of total external natural radiation	This might present difficulties as lower oxygen tension at high altitude is a complicating factor
Other high towns in South America — Quito, Ecuador — altitude 9 350 feet (2850 m); latitude 0°; population 212 873 Bogota, Colombia — altitude 8 660 feet (2640 m); latitude 4°N; population 325 658 Cerro de Pasco, Peru — altitude 13 973 feet (4259 m); latitude 10°S; population 19 187				
Himalayan area — altitude 12 087 feet (3684 m); latitude 30°N; population (Lhasa) about 20 000				

* Populations and altitudes from the Columbia Lippincott Gazetteer of the World (1952)

to the demonstration of significant genetic changes. The Committee is cognizant, however, of the desirability of obtaining meaningful data, imperfect though they may be, on the consequences of prolonged exposure to low doses of radiation. Such is the present status of knowledge of the somatic and genetic effects of chronic low-level exposures that any proper investigation of areas of high natural radiation is certain to contribute to the fund of biological knowledge and the ultimate specification of the genetic risks accruing from increasing exposure to ionizing radiations.

PRINCIPLES OF PLANNING INVESTIGATIONS OF HIGH-RADIATION AREAS

3. Type of Information Needed

Before commenting on the kind of information to be sought in studies of this nature, some general remarks should be made concerning the factors which determine the significance or "resolving power" of such a study, since they bear on the type of data to be collected.

These factors, as enumerated in Annex H of the report of the United Nations Scientific Committee on the Effects of Atomic Radiation,[1] are:

(*a*) the (cumulative) dose to the parents of the individuals under study;

(*b*) the number of individuals whose parents have been so exposed;

(*c*) the number of characteristics of genetic significance to be recorded;

(*d*) the manner in which information on these characteristics is collected;

(*e*) the availability of a suitable control population.

In view of a recent finding [2] that in the mouse fewer mutations occur in response to chronic irradiation than are caused by acute irradiation with the same dose, an added factor may be present in evaluating a study in which the dose in question is accumulated over a long time.

It is difficult to consider these factors independently of one another since, for instance, the decision as to the number (and type) of characteristics to be recorded cannot but be influenced by the cumulative dose to the parents of the individuals under study and the number of individuals whose parents have been so exposed.

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[1] United Nations, Scientific Committee on the Effects of Atomic Radiation (1958) *Report* ..., New York, p. 172 (document A/3838)

[2] Russell, W. L. & Russell, L.B. (1958) *Radiation-induced genetic damage in mice.* In: *Proceedings of the Second United Nations International Conference on the Peaceful Uses of Atomic Energy*, Geneva, Vol. 22, p. 360

3.1 Principles determining the type of information sought

Two seemingly different approaches to the study of genetic effects in areas of high natural radiation exist. On the one hand, effort could be directed toward the study of characters known to appear, or at least thought to appear, as a result of single-gene mutations. This method of study can be termed the " specific phenotype " approach, and it is assumed that each of the phenotypes chosen for study arises as a consequence of the mutation of one or a small number of genes. On the other hand, effort could be directed toward the study of those genetic characteristics of the population which it is assumed reflect the cumulative effect of mutation at many loci, such as the sex ratio. This may be termed the " population characteristics " approach. These two approaches are not necessarily mutually exclusive, and are so presented here largely for convenience. In fact, the " population characteristics " approach would under most circumstances lead to an accumulation of some information bearing on the frequencies of specific phenotypes.

In general, the genetically more appealing " specific phenotype " approach will not be feasible as it requires larger numbers of children born to highly exposed people than will be available except under very unusual circumstances. This assertion rests on two considerations. Firstly, the number of characters with simple modes of heredity which are at present known and which pose minimum diagnostic problems is limited, perhaps in the neighbourhood of 100. Secondly, it may be anticipated that the probability of a mutation per locus per unit dose will be of the order of 1×10^{-7}. Thus, the probability that any given individual will possess one or more of the requisite phenotypes is extremely small. It follows then that to obtain a sufficient number of individuals possessing the requisite phenotypes for a statistically significant result to emerge, a rather large number of observations must be made. It does not appear that the prerequisites for this approach are met by any existing population, and so in this presentation attention will be concentrated on the approach which relies on less specific indicators for the demonstration of genetic effects. Unfortunately, practically all of the less specific indicators of genetic change which it is feasible to employ are influenced by a variety of environmental factors, which makes the question of adequate controls especially critical.

The indicators which may be utilized in the " population characteristics " approach are of two types, depending on whether they emerge from the essentially non-medical vital statistics of an area, or whether they depend on medical and allied efforts in that same area.

From properly collected vital statistics, such items as birth-rates, death-rates, life expectancies, fertilities and sex ratio can be extracted, all of which may, with suitable reservations, be used as a basis for evaluating genetic differences between populations.

On the medical side, population data of especial value for the evaluation of genetic change include the frequency (and types) of congenital defects, patterns of growth and development, and morbidity and mortality data. In order that population comparisons with respect to any of these indicators of genetic difference be valid, extensive information must be available on the two or more populations concerned with respect to such matters as:

(*a*) geography of the areas occupied by the populations;
(*b*) origin of the groups in question;
(*c*) inbreeding levels;
(*d*) effective population size;
(*e*) migration;
(*f*) diet;
(*g*) cultural and religious practices affecting reproduction;
(*h*) socio-economic conditions;
(*i*) other factors influencing morbidity and mortality patterns.

Equally important, but generally less readily obtainable, is information of a historical nature bearing upon several of the above.

An extension of the " specific phenotype " approach which appears to merit exploration when comparing *large* populations, one of which is subjected to a relatively small increase in radiation exposure, involves the study of maternal and paternal " age effects " in the appearance of mutant phenotypes. Such age effects, even in the male, are undoubtedly compounded of many factors, only one of which is an increasing probability with the passage of time of induced mutation due to ionizing radiation. However, a significantly increased age effect in the population exposed to the greater amount of radiation could be construed as evidence for the induction of mutation, and a quantitative treatment derived.

3.2 The possible usefulness of studies on consanguinity effects

In populations long exposed to increased amounts of ionizing radiation, there will presumably have occurred an accumulation of induced recessive mutations. The magnitude of this accumulation will presumably depend on many factors—severity of natural selection, degree of inbreeding, etc. The possibility exists that this accumulation can be assessed by studies comparing the magnitude of consanguinity effects in this population with the magnitude of such effects in a suitable control group.

3.3 Approaches not depending on large population surveys

Several recent scientific developments, although still in need of technical improvements, appear to offer alternative approaches to those just enumerated. These approaches do not involve the surveying of large populations but the study of somatic mutation in the individual, e.g., the frequency of erythrocytes altered in their serological behaviour,[1] or the appearance of chromosome changes or altered serological or biochemical behaviour in somatic cells as studied in tissue cultures.

Whatever the contribution of these studies will be to the general problem of the effects of radiation on man, it is clear that they can only complement population studies but cannot replace them. In fact, while they will contribute to the problem of the frequency with which mutations are induced, whether they will contribute to the equally important question of the fate of induced mutations in human populations is uncertain.

4. Collection of Specific Information

In offering the following general remarks concerning the specific information to be sought, the Committee recognizes clearly the extent to which the exact details will be shaped by the particular circumstances surrounding any given study. If, however, studies in a variety of geographic areas are to be comparable, then some measure of uniformity of approach is obviously desirable. It seems reasonable to expect that such studies will differ mainly in the intensiveness of the investigation. Accordingly, the Committee urges that studies of areas of high natural radiation evolve through certain specified stages, proceeding from data easily collected by a minimum of medical personnel to a more elaborate programme where success will involve rather substantial medical support.

4.1 The different levels at which information can be collected

The Committee suggests that it is appropriate to think in terms of levels of information, the lowest level being that at which information is most readily collected although, in some instances, it may be indispensable to the acquisition of information at higher levels. At least six " levels " can be recognized:

(1) *Accurate demographic statistics*, from which can be calculated birth-rate, life expectancy, sex ratio, etc. This is essentially non-medical data, an important consideration in countries whose medical personnel are in short supply.

(2) *Growth and development data*. These can be collected at various levels of complexity, according to techniques abundantly discussed in the

[1] Atwood, K. C. & Scheinberg, S. (1958) *Science*, **127**, 1058

literature. Again, much of this information can be collected by non-medical personnel.

(3) *Patterns of congenital defect*. In the simplest form these are based on observations by physicians on all new-born infants. A re-examination at age nine months will approximately double the amount of defect observed, and a further examination at age 10 years should more than triple the number of defects for evaluation.

(4) *Morbidity and mortality patterns as based on clinical data*. With the addition of data of this type, the medical picture of the population is brought near to completion. This, again, is not an all-or-none type of observation—one can begin with certain key diseases and increase the degree of reporting as facilities expand. Moreover, in contrast to many developmental anomalies, progressive diseases such as malignant neoplasia inevitably reach a stage where they impel recognition. Early recognition, though perhaps most desirable for the welfare of the individual, may imply a much greater expenditure of diagnostic effort than is requisite for study purposes. In the studies of the type under consideration, some compromises must be made to achieve a working balance between the medical needs of the people and the available resources of the project.

(5) *Laboratory studies*. Laboratory studies are expensive, often time-consuming, and require a high degree of technical skill which may, in large population studies, confine their application to restricted samples. They are, however, more objective in their nature, and can be made practically free of any possible bias on the part of those carrying out the tests. Suitable objects of study are blood groups, haemoglobins and other genetic markers regarding the heritability of which information is being accumulated. Cytological studies on the chromosome complement of the exposed populations may also prove fruitful. In addition, laboratory services will be needed for the proper support of the studies essential for the determination of individual health status.

(6) *Necropsies*. The final level will consist of post-mortem studies on a substantial fraction of the population.

The transition from one level to the next is of course not necessarily on an all-or-none basis ; there may be a substantial degree of overlapping. Thus, under most circumstances a necropsy programme will be introduced in conjunction with efforts to obtain patterns of morbidity and mortality. In collecting data such as that under discussion, it is necessary to bear in mind from the beginning that the unit of study in genetics is generally the family, and information should be collected with a view toward family relationships.

Not enough is known concerning human genetics to permit accurate statements concerning the relative value of the various types of observations here enumerated. There are, however, increasing grounds for thinking that the sex ratio and length of life may be relatively sensitive indicators of radiation-induced mutations.[1, 2] On the other hand, congenital defects may, to a considerable degree, be the manifestation of complex genetic systems whose expression is significantly influenced by environmental variables and whose phenotypic response to increased mutation rates is complicated and at present poorly understood.[3] If this is correct, then the type of data which is most easily collected under a wide variety of circumstances may actually be that which is most pertinent to an evaluation of radiation effects. Otherwise stated, if the amount of information of genetic value which could be extracted from a population were to be graded on a quantitative scale, it might well be that by the expenditure of a certain effort 95% of the information could be extracted, whereas the expenditure of only a quarter of that effort would yield 75% of the information. Attention is again directed toward the critical role played by the control population in the final analysis of data with reference to any of these levels of information.

4.2 Classification and nomenclature of specific anomalies

If the various studies which are to be undertaken on this problem are to be comparable, one requirement is for a uniform system of nomenclature with which to record observations. For a variety of reasons, the WHO Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death (1955 revision) has much to recommend it. However, this classification is not sufficiently detailed with respect to many entities of genetic interest ; the possibility is raised that at the time of the next revision of this manual some thought be devoted to expanding certain sections to make them more useful for genetic purposes.

4.3 Standardization of anthropological measurements

The human body lends itself to a variety of measurements and ways of measuring. It is suggested that in approaching the question of the appropriate techniques to be employed, Martin's handbook[4] be used as a reference manual. Attention is directed to the fact that these measurements are overlapping rather than independent approaches to bodily proportions and development. In comparing two populations, then, the comparison

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[1] Schull, W. J. & Neel, J. V. (1958) *Science*, **128**, 343

[2] Russell, W. L. (1957) *Proc. nat. Acad. Sci. (Wash.)*, **43**, 324

[3] Neel, J. V. (1958) *Amer. J. hum. Genet.*, **10**, 398

[4] Martin, R. (1928) *Lehrbuch für Anthropologie in systematischer Darstellung*, 2nd ed., Fischer, Jena, 3 vols

of individual measurements does not easily lend itself to a clear picture of the significance of any differences which may be observed. It seems inevitable that multivariate analysis of the anthropometric data will have to be adopted. To a rather large degree, the scope of the multivariate analysis will be dependent upon the computational facilities which are available. In the absence of electronic computers, it would be inadvisable to attempt to handle more than, say, six or eight variables. The variables should be so selected as to represent both the linear and circumferential components in growth, and, further, to minimize the correlations between the measurements chosen.

4.4 Correlative studies on plant and animal material

At some point in the development of such studies, consideration must be given to correlative observations on plant and animal material. For instance, the frequency of chromosomal abnormalities in the dividing cells of long-lived plant material might be a valuable observation. The possibility of genetic studies on the local fauna, and especially on genetically well-investigated forms, such as *Drosophila* and mice, must be entertained. The possibility that organisms living in high-background areas may show an increased radiation resistance may deserve investigation.

4.5 Physical environment and dosimetry

Ultimately, the interpretation of any biological changes encountered in these studies involves an adequate exploration of the environment. Physical measurements and radiochemical analyses may be required to describe fully the radiation field with respect to : (1) intensity and energy levels of the various components ; (2) air transport of particulate material ; (3) concentration of specific radioisotopes in elements of the food chain ; and (4) determination of the body burdens and distribution of the significant radioactive substances.

Dosimetric computations made possible by precise characterization of the radioactive environment may be supplemented by direct dose measurements, utilizing the most efficient instruments available at the time. Data of the type indicated would permit later review and increasing refinement.

The dosimetric problems will vary from one area to another, depending upon the nature of the radioactive deposits ; however, it is important that deposition of radioactive substances in tissues such as those of bone or lung, which would appear to have little significance with reference to gonadal dose, should not be overlooked, as it may be of significance in the production of somatic effects.

5. Interrelationship of Genetic Studies with Work which might be Undertaken on the Somatic Effects of Radiation

It is of paramount importance in studying the effects of radiation to be able, if possible, to distinguish the purely somatic effects on the individual who is born and who lives in a radioactive environment from the manifestations of the genetic burden that may have been passed on to him as a result of previous generations of exposure. The manifestations of genetic changes are themselves, however, somatic, and it is important to remember the degree to which the measure of seemingly " pure " somatic effect turns out to involve a genetic component. Despite this interplay of genetic and somatic effects, observations on the several variables to be enumerated in 5.1 and 5.2 seem justified, since they will bear on such questions of basic interest as :.

(1) What are the forms of the dose-response curves in man at low levels of radiation with reference to such varied phenomena as leukaemia, bone sarcoma, etc. ?

(2) Are there threshold values below which somatic effects associated with radiation exposure are not observed ?

(3) When a shortening of the life-span is encountered, to what extent is it (a) a genetic effect ; (b) a direct somatic effect of radiation, possibly of greatest importance in intra-uterine life and early childhood ; and (c) a combination of both ?

5.1 Shortening of life-span

Shortening of the life-span following exposure to radiation is best studied by an examination of age-specific death-rates. The interpretation of such observations rests upon the general premise that the death-rates in a population are a reflection of the biological state of the entire population and not just something that pertains to those who die.

5.2 Other manifestations of somatic injury

The second class of somatic manifestation consists in the occurrence of specific events, such as an increase in the frequency of various tumours or of leukaemia, or the onset of some of the anaemias, which may be related to radiation injury. There are lesions such as cataracts and other ocular alterations where one can make observations which are pertinent to the question of somatic injury. Special attention should be paid to such phenomena in early childhood.

6. Statistical Considerations

An attempt to state general statistical principles applicable to the investigation of high-background areas is apt to lead either to the statement of principles so broad that they contribute nothing, or to voicing what would appear to be the obvious. At the risk of doing the latter, the Committee affirms the general principle that the most important consideration is the prior specification of the question or questions which the data can hope to answer. Aside from this general consideration, there exists a number of other statistical problems which may, to some degree, be anticipated from the nature of investigations of chronic low level exposures. These problems can be seen more clearly if one enumerates the types of variates liable to be encountered. These variates may be grouped into four classes, namely:

(1) the "*experimental*" variables, the objects of the investigation;

(2) *controlled extraneous* variables, the control being through selection of the comparison population or estimation procedures;

(3) *uncontrolled extraneous* variables which can be treated as *randomized* errors;

(4) *confounded extraneous* variables, these being uncontrolled variates intimately interwoven into the fabric of the experimental variates, so as to favour one group over another.

In a very real sense, the worth of a survey will be directly proportional to the ability to recognize and delineate these variates. Clearly in an "ideal" experiment confounded extraneous variables would not occur; either by design or randomization these variates would be controlled or become part of the randomized errors. In surveys, since it is frequently impossible or not feasible to randomize the otherwise confounded uncontrolled variates, one may attempt to select as experimental variates those characteristics of the organism which, while subject to change by the stimulus under investigation, are least influenced by other factors which may be dissimilarly distributed in the groups under study. The alternative is to attempt to separate the experimental and confounded variates through selection of the comparison population and/or recourse to multiple ways of classification, stratification, partial correlations, etc. It is unfortunate, but true, that most of the measurements indicative of radiation-induced genetic damage which are readily obtained are also influenced by a wide variety of extraneous variables, among these being such things as maternal age, size of family, and nutrition.

6.1 The value of general calculations, e.g. of the numerical criteria which comparative surveys of an irradiated and a control population would have to satisfy

From the introduction it will be evident that general calculations are apt *a priori* to have only limited usefulness. This stems from the necessity to make certain assumptions in the calculations which may or may not, in fact, be satisfied. Moreover, since as a rule, the effect of confounded variates cannot be specified in advance, the calculations are generally with respect to an idealized situation, namely, one where it is assumed that any difference which may exist between the two populations under comparison will be due to the " treatment " alone. Despite the uncertainties which surround general calculations, they may serve as a guide to intelligent planning, and afford some prior indication of the possibility of demonstrating effects of radiation or the worth of negative findings.

Perhaps the most meaningful general calculation which can be made is to determine the approximate difference between a control and irradiated population which may be demonstrable with the number of observations to be expected in a given instance. This calculation does not require assumptions regarding genetic mechanisms, selection, etc. For illustrative purposes and to provide certain figures for planning, let us assume an irradiated population of approximately 100 000 persons, that an adequate control of equal size can be obtained, and, for the moment, that the observations to be made will be based upon persons newly born. Clearly the number of observations will be a function of the yearly birth-rate, and the duration of the study (see Table 7).

TABLE 7. MAXIMUM NUMBER OF NEWBORNS IN AN INITIAL POPULATION OF 100 000 FOR DIFFERENT BIRTH-RATES AT 5-YEAR INTERVALS

Average yearly birth-rate	Population of new-borns in			
	5 years	10 years	15 years	20 years
25 per 1 000	12 500	25 000	37 500	50 000
30 per 1 000	15 000	30 000	45 000	60 000
35 per 1 000	17 500	35 000	52 500	70 000
40 per 1 000	20 000	40 000	60 000	80 000
45 per 1 000	22 500	45 000	67 500	90 000

To simplify subsequent calculations, let us assume that the study will continue for either 10 or 20 years, and that during this interval the average yearly birth-rate will be 35 per 1000. This implies, then, a total (in the combined populations) of 70 000 observations in 10 years, or 140 000 in 20. Now the difference which one may reasonably expect to detect is a function of (1) the sample size; (2) the confidence level (the frequency with which one rejects the null hypothesis when it is true); and (3) the power of the test (the frequency with which one rejects the null hypothesis when it is false). Suppose one were interested in contrasting in these two populations the frequency of some event such as the occurrence of a congenitally malformed child, the frequency of stillbirths, etc. To illustrate the differences which would be demonstrable, we shall assume (1) one-tailed tests of significance, with a confidence level of 0.05; (2) a power of the test equal to 0.90; and (3) that one will be contrasting a single exposed population with its control. If two-tailed tests were used, the necessary difference would be larger for a given proportion and sample size; conversely, if the power of the test were reduced, the necessary difference would be smaller for a fixed proportion, sample size, and test hypothesis. It should be noted that the efficiency of the study could be measurably improved if exposures could be quantified so that regression techniques might be employed in the analysis. Under the conditions previously given, the minimum differences demonstrable are approximately as shown in Table 8.

TABLE 8. MINIMUM INCREASE IN FREQUENCY OF A GENETICALLY CONTROLLED EVENT DEMONSTRABLE IN AN IRRADIATED POPULATION

Estimated frequency in control population	Minimum frequency in irradiated population demonstrably different from that in control group	
	for pop. of 35 000	for pop. of 70 000
0.001	0.0018	0.0016
0.01	0.0123	0.0116
0.02	0.023	0.022
0.05	0.055	0.054
0.10	0.107	0.105
0.50	0.511	0.508

The demonstrable difference between means or standard deviations can similarly be computed.

So far, one is on rather firm statistical footing, but as soon as one turns to the obvious question " Are these the differences we might expect on genetic grounds?", a very large element of speculation enters. From the data compiled in Hiroshima and Nagasaki [1] one would be tempted

[1] Neel, J. V. & Schull, W. J. (1956) *The effect of exposure to the atomic bombs on pregnancy termination in Hiroshima and Nagasaki*, National Academy of Sciences — National Research Council, Washington, D.C.

6.3 Sources of error and fallacies which could arise in field recording

The types of errors or fallacies which could arise in field studies can arbitrarily be divided into two groups. Firstly, there will be errors which are more or less unique to the area being studied. These could be specified in advance only by someone thoroughly familiar with the region. Most of these errors will have their roots in an imperfect understanding of the culture of the people ; and presumably a number of them would be revealed by a pilot study. Secondly, there exists a class of errors common to all large-scale studies. Only three of these sources of error are singled out for comment. The first of these is the problem of maintaining uniformity of examination when a number of examiners are employed. There is no simple solution to this, and only constant surveillance and careful indoctrination of the examiners will minimize this source of error. The second important source of error in studies on areas of high-background radiation results from the examiner knowing to which population the examinee belongs. With field recording and the differing geographical distributions of the two populations, this type of error is inevitable, especially in view of the emotionally charged atmosphere which surrounds the problems of the effects of radiation. Some idea of the magnitude of this bias might come from the inclusion in any programme of study of selected laboratory procedures which could be conducted so that the technician was unaware of the population from which the specimen was drawn. The third source of error stems from the simple fact that intensive observations can hardly be continued for any length of time without the population changing to some degree. Perhaps the change is most apt to take the form of an increased awareness on the part of the examined individual of the objectives of the study, and, as a consequence, some loss of perspective. It is possible to combat this only through a scrupulous attention to completeness of examination from the inception of the project, and the selection of the most objective, incontestable measurements possible, such as sex, anthropometric, or laboratory measurements.

7. Side Benefits from *ad hoc* Studies

It is apparent that properly organized studies of the type under discussion cannot fail to result in many contributions to human biology other than those concerned with human radiation genetics.

7.1 Opportunities for training young geneticists and other workers

The professional staff engaged in these studies will often consist of five to ten highly-trained individuals—geneticists, statisticians, physicians, etc. Opportunities will exist to provide students with a type of field experience which can be an integral part of their training for work in human genetics.

7.2 Opportunities for developing techniques for the study of populations

The techniques for large-scale studies of various aspects of human population genetics are still in their infancy. It is likely that for years to come, each large-scale study undertaken will be encountering field problems and statistical questions not previously solved. It is inevitable, then, that studies of the type under discussion will make important contributions to the developing methodology of human genetics.

7.3 Opportunities for the collection of information bearing on a variety of topics in human biology

It is difficult to envisage a study on human radiation genetics which would not yield information on a variety of other topics of interest to human biologists. Thus, in the process of making allowance for the extraneous variables mentioned in section 3, data will be collected concerning the influence of diet, ethnic background, inbreeding levels, etc., on the expression of the characteristics being utilized as indicators of radiation effects. Information will also accumulate concerning the total impact of hereditary disease on the populations under study, as well as data concerning mutation rates and other specific items of general genetic interest.

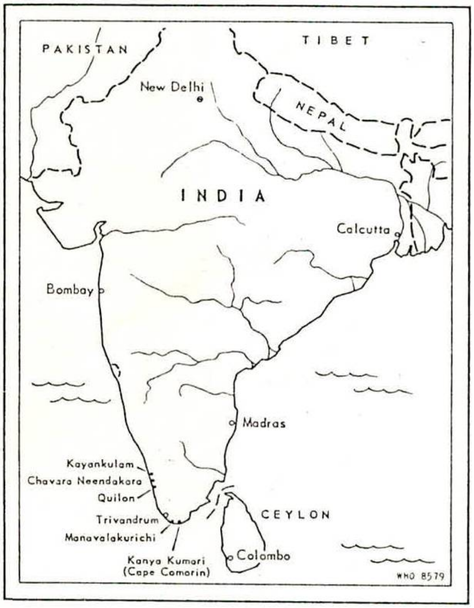
Attention is directed to the obvious problem of maintaining balance between the various components of such studies. This applies not only to the study of radiation genetics proper, but also to the side benefits to which this section is devoted.

THE KERALA PROJECT

8. Statement of the General Problem

Although there exists a considerable body of knowledge on the sequelae of effects produced by ionizing radiations on biological systems at different levels of integration, the long-term consequences to human populations exposed to continuous doses of relatively high radiation for very long periods of time, and probably extending over many generations, have not so far been studied. An ideal milieu for such studies would be a region which is well populated and where, at the same time, the radiation field is significantly higher than the normal background. A nearly unique situation exists in parts of Kerala and Madras States in the southernmost region of the west coast of India. Here, along the coastal belt stretching over a hundred miles in length and about a quarter of a mile in width from near Kayankulam to Kanyakumari, interrupted deposits of ilmenite sands containing radioactive material occur (Fig. 1). The radioactivity of the sands is due to the monazite component which contains thorium and to a limited extent uranium, along with several other rare earth minerals, such as rutile, sillimanite, zircon and titanium-bearing ores. The thorium content ranges from 8% to 10.5% as against 5-6% in the Brazilian monazite deposits.[1] Most of the radioactivity (95%) arises from thorium and its decay products.

FIG. 1. POSITION OF THE KERALA AND MADRAS MONAZITE REGIONS



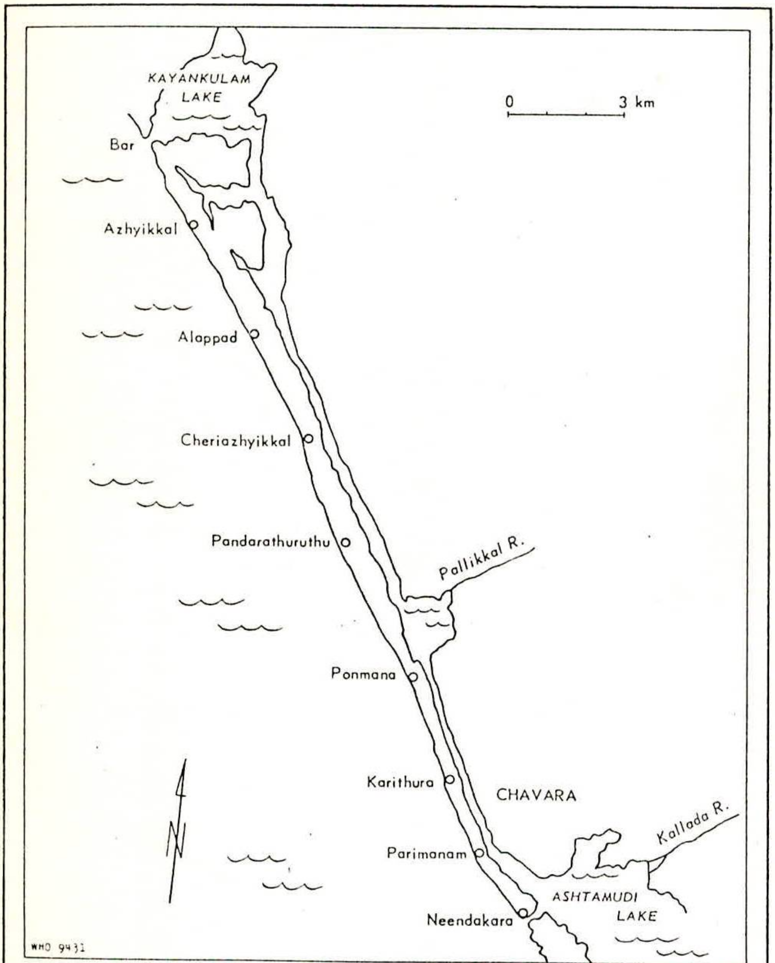
The importance of the Kerala and Madras monazite regions stems from the fact that the population (estimated in the region of 80 000, living in a radioactive milieu, is subjected to low-level chronic irradiation and presumably has been so exposed for generations. The two regions to be studied are rather well defined—the Chavara-Neendakara and Manavalakurichi—and comparable control regions exist in nearby areas (see Fig. 1-3).

It has already been pointed out [2] that, whereas most peoples receive an average whole-body background radiation from all natural sources of about 3 r per person per 30 years, these populations are estimated to receive 10-15 times as much ionizing radiation. While further physical monitoring is needed to establish more accurately the doses being received, it seems clear that these estimates are likely to be reasonably accurate.

[1] More recently, bigger deposits of monazite have been discovered in the Indian State of Bihar. No measurements, however, have been carried out.

[2] Gopal-Ayengar, A. R. (1957) Possible areas with sufficiently different background-radiation levels to permit detection of differences in mutation rates of "marker" genes. In: World Health Organization, *Effect of radiation on human heredity*, Geneva, p. 115

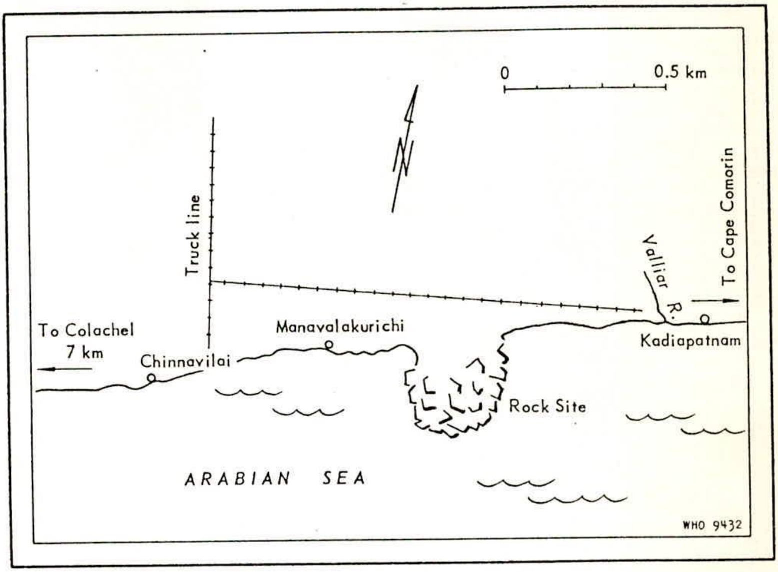
FIG. 2. THE CHAVARA-NEENDAKARA AREA



It should be noted that the excess amount of radiation being received by these populations in Kerala and Madras States is, according to present estimates, within the range of that necessary to double the mutation rate.

Such excess radiation per generation is at least several times greater than is likely to be received on the average by any substantial number of

FIG. 3. THE MANAVALAKURICHI AREA



people elsewhere from the sum of natural background radiation, together with the total of artificially-produced radiation on the present scale.[1, 2]

8.1 The two areas where the sand beaches contain monazite, and the people living there

8.1.1 *The Chavara-Neendakara area*

This beach is in Kerala State. It extends from the outlet of the Ashtamudi Lake up to Kayankulam Lake, about two miles north of the village of Azhyikkal. The strip is an island, as the two lakes are joined to the landward side of the beach by a canalized lagoon. The area isolated varies from a few hundred yards in width in the south to over a mile in the north. It is convenient to call this the Chavara area, from the name of a large village and district in the south of the strip. The form and position of the area may be seen from Fig. 2. The ilmenite deposits have a rather patchy distribution up and down the coast, partly by reason of varying deposits by currents, and partly by reason of extensive removal

[1] Great Britain, Medical Research Council (1956) *The hazards to man of nuclear and allied radiations*, London

[2] World Health Organization (1957) *Effect of radiation on human heredity*, Geneva

of the richest ilmenite deposits over the past 30 years by three mining companies. The distribution may also be affected by the violence of the previous monsoon. Off the beach there is much sand lying in pockets and the whole hard area has a surface covering of sand with very variable monazite content.

This area is inhabited by not less than 60 000 people. The great majority live by fishing. About half are Christians (Roman Catholics) and the rest Hindu. There are a few Mohammedan fish traders but not all live on the strip, most only come each day to bring fish.

The Christians and Hindus speak the same language (Malayalam) and are obviously of the same stock. Superficially at least there is no difference in their general environment, diet, or economic circumstances. Among the Christians, consanguineous marriages may occur less frequently. Among the Hindus, there is matriarchal exogamy so that a man seeks a bride from another " gotra ".[1] It is preferred that a man should marry his full cousin who is his father's sister's daughter (and therefore would probably be brought up in another village). Among Hindus, the full-cousin marriage rate is believed to be about 10-20 per cent. Hindu-Christian marriages are said never to occur.

Christians and Hindus alike are friendly and cheerful. The percentage of literacy is very high. Accurate estimates of the live-birth rate are not at present available for the area, but a number of indications suggest that it is over 30 per 1000 of the population. Although stillbirths are supposed to be registered, it is clear that there are many which are not, and probably only those attended by the midwives or the few occurring in the Indo-Norwegian Hospital at Neendakara are consistently recorded. Prematurity is said to be very uncommon, but there are no data to support such a contention. It would be reasonable to expect in such an area a prematurity rate (on the weight standards of 2500 g) of 10-15% of total births, a stillbirth rate of about 50-60 per 1000 live and stillbirths, and an infant mortality of the order of rather more than 100 per 1000 live births. Such scanty data as are at present available have suggested lower figures than any of these, but they are almost certainly underestimates.

Selection of a control area having a population with the same religious distribution and way of life, and following the same occupations (except with regard to the sand-processing companies), should not be unduly difficult. The same fisherfolk occupy the seashore villages north and south of the area. To the south, however, the urban fringe of the town of Quilon impinges, bringing an inevitable alteration in the population characteristics. Consequently, a defined strip north of the Kayankulam Bar would probably be most suitable as a control area. In the absence of a canal, the control area could not be as conveniently defined as the monazite sand area, but

[1] See section 8.1.2.

there should be no insuperable difficulties.. A small gap even of a mile or two north of the monazite area might well be left out of the control area so as to minimize the number of transfers between the area and of marriages between people in villages in the study and control areas. Again, only careful study would confirm the value of such a suggestion.

8.1.2 *Manavalakurichi area*

This area of monazite sand is located some 40 miles south of Trivandrum. The area is not in Kerala but in Madras State. It is even more densely populated than is the first area. It is about one mile long from the mouth of the river Valliar to Chinnavilai village and has about 11 000 to 12 000 inhabitants in the beach villages. Again, some are Roman Catholics and the others Hindus (roughly 50 : 50).

Most of the general remarks about the Chavara area are applicable here also and need not be repeated. All are of Tamil stock and speak that language. The pattern of mating of the Tamil Hindus is different from that of the Malayalam-speaking Hindus in the Chavara area. There are a number of " gotras ", exogamous sections or sub-groups, each bearing the name of a supposed ancestor in the community. A man can only marry into a certain number of specified, exclusive sections, and his sisters can only marry into a different group of sections.

The area is more difficult to define than Chavara but boundaries can be set. North and south of the area there are Tamil-speaking people, apparently of the same ethnic origin. A suitable control population for study would not be unduly difficult to find.

9. Physical Aspects

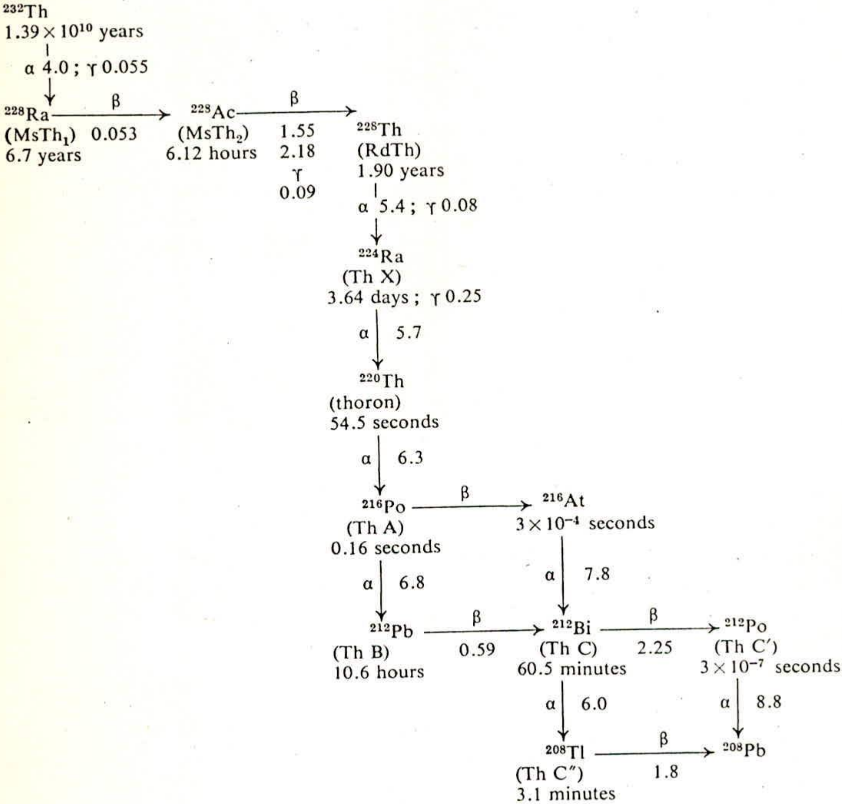
By way of introduction to a presentation of the physical aspects of the Kerala project, a summary is presented of the properties of thorium and its daughter products.

Thorium, the element of atomic number 90, is widely distributed throughout the earth's crust, but appreciable concentrations occur less frequently than in the case of uranium. It is the parent element of one of the naturally radioactive series, decaying by alpha emission, the daughter substances further decaying by beta and gamma emissions. The accompanying chart (p. 29) shows the most important features of the chain of transmutations, with the associated energies and the half-lives of the products. As in the case of the other series, the end-product is a stable isotope of lead, in this instance ^{208}Pb.

From the biological standpoint, there are only two daughters that have half-lives of sufficient length to give rise to problems. These are ^{228}Ra

THE THORIUM FAMILY

(Energies in Mev)



(mesothorium 1) with half-life of 6.7 years and ^{228}Th (radiothorium) whose half-life is 1.9 years. Since ^{228}Th is isotopic with the parent ^{232}Th, it will exhibit the same chemical behaviour. This is in contrast to ^{228}Ra which behaves chemically as common ^{226}Ra but has a much greater radioactivity associated with its shorter half-life. ^{228}Ra behaves in the body in a similar manner to calcium.

The most commonly found thorium-containing minerals are silicates and phosphates in combination with several rare earths. Some deposits of the oxide are known, reflecting the insolubility of this compound. Many of the salts of thorium, such as the chloride and nitrate are readily soluble in water.

9.1 Probable gonad dose from gamma radiation

Three sample surveys of the monazite areas of Kerala and Manavalakurichi have been carried out, or are being carried out, by the Health Physics and Air Monitoring Divisions of the Department of Atomic Energy, Government of India, to estimate the internal and external radiation exposures of the population in the coastal areas. The first of these studies was carried out in 1956,[1] the second in 1957,[2] and a third is at present being completed. Only a summary of the findings is given here.

Inspection of Table 9 reveals a twenty-fold variation in the average gamma activity over the 10 villages in the surveys. The average gamma field to which an individual residing in these areas is being subjected is computed as follows :

$$\text{average} = \frac{{}_r\Sigma P_r X_r}{{}_r\Sigma P_r}$$

where P_r = the total population of village r

and X_r = the average gamma activity of village r in millirads per year, as given in Table 10

The average so obtained is 1300 millirads per year.

In order to determine the total activity due to beta and gamma radiation, use was made of the data obtained in the earlier survey (1956), in which both the gamma and the (beta + gamma) counting rates were simultaneously obtained. It has been calculated that the contribution from beta rays to the total field was about 16% of the gamma contribution. Thus, the average total field is about 1500 millirads per year.

Three observations are pertinent to the interpretation of the potential biological significance of the above figure. Firstly, although in normal circumstances the beta dose could be considered to have a negligible effect, the fact that the decay products of thorium, mesothorium 2 (2.18 Mev), and thorium C (2.25 Mev) are high-energy emitters should not be lost sight of, especially when it is considered that the people come into close contact with the surface of the soil every time they sit or sleep on it. Secondly, it must be pointed out that the fishermen who largely inhabit this area spend a major portion of their days out at sea where the radiation level can be considered to approximate the normal background. The average dose to which the population in this area is subjected can be

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[1] Gopal-Ayengar, A. R. (1957) Possible areas with sufficiently different background-radiation levels to permit detection of differences in mutation rates of "marker" genes. In : World Health Organization, *Effect of Radiation on Human Heredity*, p. 115

[2] Bharatwal, D. S. & Vaze, G. H. (1958) *Radiation dose measurements in the monazite areas of Kerala State in India*. In : *Proceedings of the Second United Nations International Conference on the Peaceful Uses of Atomic Energy*, Geneva, Vol. 23, p. 156

TABLE 9. SUMMARY OF THE RESULTS OF SURVEYS OF THE MONAZITE AREAS OF MANAVALAKURICHI AND NEARBY REGIONS

Name of village	Population	Type of house *	Number of houses scanned	Average gamma activity in millirads per year †
Kadiapatnam	6 000	B C	7 12	2814
Manavalakurichi	11 000	A B C	15 18 3	2164
Muttam	6 000	A B C	6 5 13	736
Midalam	10 000	A C	20 20	1573
Villingem	10 000	A B C	10 9 3	131
Karamanal	2 000	A B C	6 7 6	1283
Kovalam	1 000	C	1	814
Kullatoor	2 000	A B	4 6	370
Vettoor	3 000	B	10	527
Varkala	1 000	A	12	138

† Mean of all readings taken in the village
* See below

construed, then, at a level which is lower than the measured 1500 millirads per year. Finally, rather wide variation in exposure exists in any given locality; this is, in part, a function of the extent to which the monazite sands are incorporated into house construction. The effect of an individual's type of house upon the exposure he may experience will be treated in some detail in the next section.

9.2 Variation in exposure from house to house

The people of the coastal regions usually live in small and more or less closed huts. These are mainly of three types, a brief description of which is given below:

Type A

This type of house usually has two to three rooms with a courtyard. It is fenced on all sides by a low mud wall. The single-storeyed structure has walls and floor of brick and cement. The roof is of either tile or bricks located on a wooden structure. The rooms are provided with windows and have good ventilation. The living habits of the inhabitants of this type of house are generally hygienic. The people sweep and clean the floor often, but make liberal use of the sand for flooring and for piling about the roots of coconut trees in the compounds. This type of house constitutes about 15% of the residential structures. .(The average floor space may not exceed 150 sq. ft.)

Type B

The type B house consists of one or two small rooms, with an occasional courtyard attached. The walls and floors are of mud and the ceiling of tiles. These houses do not usually have windows and are therefore poorly ventilated. Most of the houses which are built on the outskirts of a village or town have coconut trees growing in the compound, and monazite sand is used liberally around their roots. 60% of the houses belong to this category.

TABLE 10. MAXIMUM AND MINIMUM GAMMA LEVELS IN THE THREE TYPES OF HOUSES

Type	Maximum gamma level	Minimum gamma level
A	3000 mrad/year	53 mrad/year
B	3200 mrad/year	105 mrad/year
C	4000 mrad/year	145 mrad/year

TABLE 11. NUMBER OF SURVEYED HOUSES OF EACH TYPE SHOWING DIFFERENT ACTIVITY LEVELS INSIDE

Number	Gamma activity in millirad per year	Number of A type houses	Number of B type houses	Number of C type houses
1	Above 3000	0	1	7
2	Between 2500 and 3000	2	8	3
3	Between 2000 and 2500	8	13	4
4	Between 1500 and 2000	18	5	15
5	Between 1000 and 1500	11	1	9
6	Between 500 and 1000	6	11	17
7	Below 500	28	23	3
	Totals	73	62	58

Type C

These are shack-like structures, about 10 ft in height, built out of bamboo and palm leaves, the floor being covered with sand or thick coats of mud.

Table 10 shows the maximum and minimum gamma levels encountered in the three types of huts described above.

In Table 11 is given the distribution of the surveyed houses of the three types in different activity zones.

The weight to be given to the structural differences between these three types of houses in appraising individual exposure is a perplexing problem. It will be the aim of future surveys to provide additional information pertinent to this point.

10. Radiobiological Aspects of Thorium and Daughter Products: Possibility of Gonad Dose being Produced from Internal Deposition of Radioactive Elements

While precise figures with respect to the body burdens and distribution of the significant radioactive substances are not at present available for individuals within the Kerala and Manavalakurichi areas, observations do exist regarding the possibility of a significant gonad dose being produced from the internal deposition of radioactive elements. Since certain of these observations have not yet been published, the evidence for concluding that a significant gonad dose from the internal deposition of radioactive elements is improbable is presented here in some detail.

10.1 Considerations of chemical toxicity

Thorium is an element of generally low toxicity. Under ordinary circumstances there is little transport to the tissues from the external environment. Salts of thorium as well as the oxide, when ingested, remain in the content of the gastro-intestinal tract and are excreted in the faeces with almost no absorption. Dusts, when inhaled, are for the most part passed through the intestinal tract without absorption. Following prolonged inhalation of thorium-containing dusts formed from the nitrate, fluoride, oxide, and oxalate, a variety of laboratory animals (rats, guinea-pigs, rabbits, dogs) failed to show any pathological changes save for minor changes in the white blood-cell count and in the bone-marrow.

A study of the employees in a thorium refinery[1] which had been in operation for over 30 years, and where exposures were considerably in

[1] Albert, R. et al. (1957) *A.M.A. Arch. industr. Hlth*, **11**, 234

excess of the acceptable standards for uranium, disclosed no evidence of overt industrial disease attributable to thorium.

When thorium salts are injected, acute toxicity is usually determined by the anion rather than by the thorium. The oxide is so inert that an LD_{50} cannot easily be determined; it has been widely used in colloidal form for roentgenography, especially of the liver and spleen. Thorotrast, injected intravenously, is promptly phagocytized by the reticuloendothelial cells, especially of the two organs mentioned. The material remains relatively fixed in these tissues, but over a long span of time there is a slow movement of the material with secondary deposition in more distant organs, especially the bone-marrow.

In patients who had received thorotrast many years previously, diffuse fibrosis of the liver, spleen, lymph nodes, and bone-marrow has been found. In one case, a carcinoma of the liver developed 15 years after the patient received thorotrast. The tumour showed a massive accumulation of thorotrast.

Following the injection of salts of thorium into muscles or connective tissue, the thorium is generally retained at the site of injection and only slowly released into the circulation. This movement is much slower than in the case of radium.

Once thorium compounds have been absorbed, they are excreted very slowly; for practical purposes it can be said that once within the body proper, thorium is retained indefinitely.

Following injection of the chloride in the rat, the greatest amounts are to be found in the skeleton. The preferential movement of thorium to the bone continues throughout the periods of observation reported. In a study by Lanz et al.,[1] 47% of the total was in the bone 64 days after injection of the chloride in the rat. The next greatest site of concentration, on a gram basis, is the kidney.

10.2 Considerations of radiological toxicity

The radiological aspect is of far greater significance than the purely chemical consideration of toxicity. As indicated before, the first disintegration step from ^{232}Th is the formation of mesothorium or ^{228}Ra. As a radium isotope, this is stored more avidly in bone than is thorium.

Studies in a laboratory worker accidentally injected with ^{227}Th freshly extracted from an equilibrium mixture with ^{227}Ac have been illuminating with reference to the behaviour of the daughter ^{223}Ra. Using the whole-body counter and taking advantage of the fact that all of the gamma photons over 300 kev are derived from the ^{223}Ra, it was possible to make

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[1] Lanz, H. et al. (1946) *The metabolism of thorium, protactinium and neptunium in the rat* (US Atomic Energy Commission, document MDDC-648)

good estimates of both ^{227}Th and ^{223}Ra in the body and to obtain excretion data up to 221 days.[1]

There was a marked preferential excretion of radium over thorium, so that from 33 days onward the activity ratio of Ra to Th was approximately 15% of the value expected upon purely physical grounds. Most of the excretion of both radium and thorium was by way of the faeces.

In this and other studies, radium retention was found to be described by the expression :

$$\text{Retention} = 0.3\ t^{-0.7}$$

where t is expressed in days. The retention is clearly the resultant of both radioactive decay and metabolic elimination.

Similar studies in dogs, using ^{228}Th by injection and following the behaviour of the ^{224}Ra daughter, showed that the latter behaved as though it were being continuously injected intravenously, yielding constants for the retention somewhat at variance with those in the human case.

Further theoretical studies by the Argonne National Laboratory Group [2] have been based upon the following assumptions :

(1) thorium is administered only once in the complete absence of its daughters ;

(2) no thorium is eliminated by the mammalian body ;

(3) the radium daughter produced by the thorium parent behaves as though it were injected into the blood-stream.

The third assumption leads to the adoption of the following equation for radium retention R(t) at time t in days :

$$R(t) = At^{-b}$$

for $t \geqq 1$, where A and b are constants and, to a first approximation, $A = 1 - b$. The validity of the general form of this equation has been amply verified for radium injected intravenously in several species.

The second assumption is based upon the negligible excretion found in many different experiments. A single factor would seem to represent the thorium retention satisfactorily.

Since the calculations appear to fit the data in the cases of the pairs of gamma-emitting isotopes studied, it seems reasonable to extend the calculation to $^{232}Th - {}^{228}Ra$ and to $^{228}Th - {}^{224}Ra$. The calculated activity ratios for selected times for these two pairs are shown in Tables 12 and 13.

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[1] Gustafson, P. F. et al. (1955) *Thorium-227 Accident*. In : Argonne National Laboratory, *Quarterly Report, October 1955* (document ANL-5486)

[2] Reynolds, J. C., Gustafson, P. F., Marinelli, L. D. (1957) *Retention and elimination of radium isotopes produced by the decay of thorium parents within the body — calculations and comparison with experimental findings* (Argonne National Laboratory, document ANL-5689)

TABLE 12. ACTIVITY RATIO [A(t)] OF ^{232}Th TO ^{228}Ra AS A FUNCTION OF TIME

b = 0.3		b = 0.5		b = 0.7	
t(days)	A(t)	t(days)	A(t)	t(days)	A(t)
8.86	0.00126	7.48	0.000692	5.80	0.000358
29.5	0.00297	24.9	0.00133	19.3	0.000558
88.6	0.00643	74.8	0.00235	58.0	0.000832
295	0.0146	249	0.00429	193	0.00124
590	0.0230	499	0.00596	386	0.00153
1 480	0.0397	1 250	0.00886	966	0.00198
2 950	0.0556	2 490	0.0113	1 930	0.00232
4 430	0.0644	3 740	0.0127	2 900	0.00250
5 900	0.0697	4 990	0.0135	3 860	0.00261
10 300	0.0762	8 730	0.0144	6 760	0.00275
14 800	0.0778	12 500	0.0147	9 660	0.00280
30 000	0.0783	30 000	0.0148	30 000	0.00283

TABLE 13. ACTIVITY RATIO [A(t)] OF ^{228}Th TO ^{224}Ra AS A FUNCTION OF TIME

b = 0.3		b = 0.5		b = 0.7	
t(days)	A(t)	t(days)	A(t)	t(days)	A(t)
2.21	0.251	1.87	0.178	1.45	0.118
4.42	0.363	3.73	0.242	2.89	0.151
6.63	0.426	5.50	0.277	4.34	0.169
8.83	0.463	7.47	0.297	5.78	0.179
15.5	0.508	13.1	0.323	10.1	0.193
22.1	0.520	18.7	0.330	14.5	0.197
30 000	0.524	30 000	0.333	30 000	0.200

10.3 Considerations from thorotrast injections

When thorotrast is injected, it is largely held in the reticuloendothelial system of the liver and spleen. It is found that approximately $^2/_3$ of the ^{228}Ra produced is retained with the phagocytized thorotrast and only about $^1/_3$ enters the blood stream and is available for translocation. The

^{228}Ra which is released from the thorotrast deposits is redeposited in the skeleton.

On the basis of the quantitative information at present available, a person who has carried a body burden of 4 g of ^{232}Th as thorotrast for several years should have the following range of activities (in curies) in the skeleton :

Minimum :

$$1.8 \times 10^{-9}\ {}^{228}Ra + 1.8 \times 10^{-9}\ {}^{228}Th + 1.9 \times 10^{-8}\ {}^{224}Ra + 1.7 \times 10^{-8}\ Em$$

Maximum :

$$1.8 \times 10^{-9}\ {}^{228}Ra + 5.5 \times 10^{-8}\ {}^{228}Th + 3.7 \times 10^{-8}\ {}^{224}Ra + 3.3 \times 10^{-8}\ Em$$

Considering the energy delivered to the bone by these activities in comparison with the 11 Mev per ^{226}Ra disintegration, these limits are approximately equivalent to 40% and 100% respectively of the dose from the presently accepted maximum permissible level of 0.1 microgram of ^{226}Ra.

Where the thorium has been acquired in soluble form permitting dispersion through the tissues, it may be anticipated that the above range of bone activity will be achieved by a little over 1 g of ^{232}Th total body burden.

10.4 Gonadal exposure from internally-deposited thorium

From all the foregoing, certain conclusions may be drawn concerning the gonadal exposure resulting from internally-deposited thorium. By any route of acquisition other than direct injection into the gonads, secondary deposition of thorium compounds in the testis and ovary is negligible, even following thorotrast injections. Gonadal exposure can therefore occur only from the gamma emission of the daughter products held in the skeleton. Since the partition of energy between gamma and alpha plus beta emissions is similar in the thorium series to that of radium plus its daughters, it appears to be approximately true that for a gonadal exposure equivalent to that resulting from the maximal permissible body burden of radium for occupational purposes, the huge amount of 4 g of thorium as thorotrast, or 1 g of the element as a soluble compound, would be required. Even in this extreme case, we would be considering a lifetime dose of a few roentgens, certainly less than 10.

11. Suggestions for Information Which Should Be Collected in a Kerala Project

To provide the appropriate perspective for the suggestions of the Committee, it should be stated that the Committee was primarily concerned with the first stage of collection of information, namely, the *ad hoc* census, and to a less extent with the procedures to follow this census. The Committee wishes to emphasize the tentative nature of the suggestions which follow.

11.1 The *ad hoc* census

There was general agreement that the first step in the Kerala study should be to select control populations as nearly comparable to the exposed populations as possible, and, as soon as reasonably convenient, to define certain essential characteristics of these populations by a census procedure. Clearly, to a considerable extent the suitability of a population chosen as a control will only be known after an *ad hoc* census. However, it may well be necessary to make a rather arbitrary choice of control areas (bearing in mind the principles set out in sections 4 and 6 of this report), rather than delay the selection until the characteristics of the exposed population are more completely revealed by a census. The advantages derived from conducting the census of the control and exposed populations as nearly concurrently as possible offset to some extent the disadvantages of having to select the control population before adequate characterization of the exposed population is available. Such is the nature of the present problem, however, that modifications may have to be subsequently made in the composition of the control population, irrespective of when it is selected —a point of importance not only in terms of effort and finance but in further underlining the need for census-taking at a relatively early stage.

Attention should be paid to the matters of size and geographic distribution of the control populations. In particular, there may be merit to distributing, if possible, the control population for a given exposed population over several geographic areas. The extremely high population density existing in the study area could be troublesome if the control population does not have the same density. This might be offset to some degree by obtaining, as control, observations at a variety of population densities. In practice, of course, due regard would have to be paid to the practical difficulties associated with suggestions of this type.

11.1.1 *The timing of an* ad hoc *census*

As regards the timing of an *ad hoc* census, it was fully realized by the Committee that local circumstances and local knowledge of the response of such communities to questioning must determine what preparations are essential. At present, the major preliminary work would seem to be (*a*) accurate mapping of the geographical areas involved ; (*b*) training of the census-takers ; (*c*) publicity efforts designed to enlist the maximum support of the populations ; and (*d*) the study of the social and cultural pattern of these populations with special reference to factors pertinent to this investigation. It was stressed, however, that there were many factors which favoured as early a census-taking as feasible. Thus, it seemed important to have basic population information before any steps were taken to increase medical care in the study areas. Moreover, to a considerable extent the planning and execution of subsequent stages of the investigation will be dependent upon the information collected by the *ad hoc* census concerning individuals, families, and the population as a whole.

11.1.2 *The form of the* ad hoc *census*

With reference to the form of the census, there seem to be many advantages in keeping to the conventional pattern of census-taking which has two essential features : (*a*) a census of those living in each house and the specification of a " head of household " ; (*b*) a census of individuals, giving the information basic to the needs of demography, and a specification of the relationship of the individuals within a household to the head of the household.

An important disadvantage of following this plan too closely is that the basic unit in genetics is the family, and even on the narrowest definition of the family the members do not necessarily live in the same house. This difficulty can be surmounted, in part, by designing the census procedure in such a way that the children of a given parent can be identified. The exact method by which this is to be done and the extent to which sibships, half-sibships and other degrees of relationship may then be constructed, will depend on local considerations regarding name frequency, and also on the information required for the precise identification of each individual within the populations.

11.1.3 *The information to be collected at the* ad hoc *census*

If a conventional census procedure is adopted, the next questions which must be dealt with are (*a*) how much information additional to normal census requirements would it be desirable to have at this stage, and (*b*) how much of this is it practicable to collect, bearing in mind considerations of time and the state of general and special education of the actual census staff ?

It was the consensus of the Committee that the following list represented the minimum information to be obtained on *each* individual and *each* household.

Individual

(1) Reference serial number
(2) Name of individual and names of father and mother

(3) Sex
(4) Language
(5) Religion
(6) Date of birth
(7) Places of birth of individual and his or her parents
(8) Age
(9) Marital status
(10) Gotra
(11) Occupation
(12) Educational attainments
(13) Consanguinity of parents (give details)
(14) Whether one of twins, triplets, etc.

If married, then:

(15) Relationship to spouse (give details)
(16) Age at marriage
(17) Living male children
(18) Living female children
(19) Age of spouse at marriage

If a woman, then:

(20) A complete roster of *all* pregnancies, including age of mother at the termination of each pregnancy, anomaly in offspring, death of offspring, stillborn infants, and those pregnancies terminating in a miscarriage or abortion.

Household

(1) Area number (from previous governmental censuses)
(2) House number (from previous governmental censuses)
(3) Village
(4) House map reference
(5) Type of house by construction (A, B or C)
(6) Some measure or measures of social and hygienic status
(7) Date of visit
(8) Name of visitor
(9) A roster of persons normally living in the house beginning with the eldest male (unless he is not related to the family). This roster is to include, for each individual, personal serial number, sex, year of birth, age, name, seen or not seen, and a family tree showing relationship to the head of the household.

It was agreed that certain items in the above list would have to be subsequently checked and expanded; notable in this respect is the information on consanguinity, reproductive performance of the mother, and migration.

11.2 The collection of demographic data following the completion of the *ad hoc* census

It was recognized that a system would have to be devised to maintain the accuracy of the demographic and reproductive performance statistics of these areas at a high level over a considerable number of years. This would involve constant combing of the population to detect failures or inaccuracies in the reporting of births, deaths and marriages: in this connexion, the principles involved in organizing "census tract areas" are relevant. The possibility was discussed of utilizing Catholic church records as a source of information and as a means of detecting breakdowns in the registration system.

11.3 Other steps to follow the *ad hoc* census

As here envisaged, the *ad hoc* census is primarily a device by which to characterize the study populations and to afford a basis for the efficient planning of subsequent stages in the investigation. Obviously then, the *ad hoc* census must be supplemented by certain other steps. Among these are the following:

11.3.1 *The checking and elaboration of certain information collected at the* ad hoc *census*

In the *ad hoc* census, practical considerations will prevent the collection of such further information regarding individuals and their relationships as would require "follow-up" visits to their houses. However, since, as presently envisaged, every individual in the population will ultimately be interviewed and examined, the census information could be checked and supplemented at the time of this interview. At this stage, family relationships should be checked and recorded in some pedigree or equivalent form so that not only degrees of consanguinity but the specific relationships which have contributed to these degrees are recorded as exactly as possible.

This interview could also serve to provide a medical or family history with respect to certain items of interest.

11.3.2 *Examination of individuals and recording of variables*

Any consideration of the type of physical examination is immediately beset by questions regarding (*a*) the objectives of such an examination and (*b*) how these objectives can be reached with the personnel likely to be available. As already noted, the objectives are to record (*a*) segregating characters—morphological, physiological, or biochemical—and (*b*) continuously distributed characteristics. Recording of the former requires, in general, a level of training not required in the latter.

An enormous number of physician hours would be consumed by physical examinations sufficiently complete to record the bulk of segregating characters. It is virtually certain that sufficient physicians would not be available for a programme so based. However, there are the so-called screening procedures that have been designed to reject people unsuitable for certain tasks, e.g., entrance into the Armed Forces or industry, or to pick out, for treatment or for more elaborate investigation, individuals with certain diseases and disorders. Similar procedures might well be developed for use in the Kerala project to screen out segregating characters. A pilot study on the lines suggested below should reveal the worth of this suggestion (it will be noted that the screening efficiency would be susceptible to test in various ways).

The dominating factor is a shortage of medical manpower. It seems likely that there are available qualified nurses with further training in midwifery and public health. Experience has shown that in school health examinations the efficiency of suitably trained nurses in recognizing defects is high, e.g., in New York City and in New Zealand. Some such scheme as follows might therefore be used. First, groups of nurses would be trained in the exact procedures required and tested for their efficiency. Each individual in the population would then be interviewed by such a trained nurse ; she would have with her the census record and would check and complete it along the lines previously suggested.

She would then :

(1) Record certain characteristics, probably (*a*) specified anthropometric measures, (*b*) colour vision, and (*c*) visual acuity.

(2) Make a standard examination directed toward revealing any general abnormality or peculiarity. This examination would include a systematic inspection of each part of the body ; all negative findings would be recorded and all anomalies, diseases or disorders would be described. There would be a standard record sheet.

(3) Place a suitable mark on the record sheet of any person exhibiting an anomaly or other positive finding or use some other device to ensure that he was referred for more detailed examination by a physician. It should be noted here that even diseases obviously caused by environmental factors, such as trachoma or scabies, should be recorded, but in view of their frequency, patients need not necessarily be referred to a physician for assessment, but only to a dispensary for treatment.

With reference to item (2) above, it is suggested that observations might be recorded with respect to :

(*a*) any obvious abnormality of physique or bodily conformation ;

(*b*) any obvious general syndrome ;

(*c*) abnormalities of skeleton and extremities, mouth, ears, skin, hair, nails, eyes, or central nervous system (palsies or ataxias).

There remain many procedures by which important variables could be detected but which require special skills or which would be too time-consuming to apply to every individual in the population. It would seem that the most likely approach would be by *ad hoc* sampling procedures. Attention is drawn to the following :

(*a*) skilled ophthalmological, neurological, dermatological, and other special examinations ;

(*b*) urine studies (e.g., for sugars, porphyrins, phenylketones, etc.) using chromatography techniques ;

(*c*) blood studies using haematological, serological and electrophoretic techniques.

The Committee was of the opinion that it would greatly increase the co-operation of the population with respect to the procedures just outlined if clinical facilities for the diagnosis and treatment of certain common diseases prevalent in the area, such as helminthic infestations, scabies, and especially trachoma, could be set up as early as is consistent with the objectives of the *ad hoc* census.

11.4 General remarks

Certain particulars of the methodology of census-taking have been considered above ; it seems appropriate, by way of concluding this section, to consider briefly the somewhat broader methodological problems raised by the Kerala study. This report has repeatedly stressed the desirability of conducting investigations of high-radiation areas in a manner whereby data from a number of these studies may be compared. For this to be meaningful requires a measure of uniformity. The Committee would urge, therefore, that where available, internationally accepted procedures of measurement be employed. Thus, the *ad hoc* census should, to the limit feasible, be conducted along the lines suggested in the *United Nations handbook of population census methods*.[1]

The Committee would also call attention to the fact that the Kerala study may well establish a precedent for subsequent studies in other areas

[1] United Nations (1954) *Handbook of population census methods*, New York

and that due consideration should therefore be given to the adoption of measurements and methods potentially applicable elsewhere.

12. Suggested Requirements in Men and Material

As presently envisaged, the Kerala study would proceed through a series of well-defined steps, from the initiation of a programme of collecting demographic statistics to, ultimately, a medically supported effort to characterize the patterns of morbidity and mortality obtaining in this area. It is convenient, therefore, to view the resources in men and material required in terms of the successive stages in the evolution of the study.

12.1 The *ad hoc* census

This should be completed, if at all possible, within a period of one month : an adequate staff should be available with at least five inspectors. The exact number of staff might be determined by a pilot survey.

The census workers must have a good education and considerable coaching in census methods. It would be advantageous to be able to employ them on subsequent work in maintaining the accuracy of the vital statistics, and, possibly, in some of the screening procedures such as simple anthropometry and checking of census information.

12.2 The on-going registration of births and deaths

It seems reasonable to expect that some 8000-9000 registerable events will occur within the study populations in any given year. The staff necessary to record these events (births, deaths, and possibly marriages) will depend largely upon the number of registration centres. If a single centre is maintained in each study area, three clerks should be able to handle the work load anticipated for any given area.

12.3 Processing of the vital statistics

Possibly 10 clerks or stenographers would be needed for coding, code checking, and mechanical analysis procedures. The precise number will depend, however, upon whether these operations occur within the study areas, or in some more centrally located area such as Trivandrum.

12.4 Screening examinations and medical support

The problem of medical manpower is clearly going to result in a compromise, there being no likelihood of the availability of more than a limited number of men and women. Much could be done, however, by planning the screening procedures well, so that the doctor's special skills were not employed on work which could be satisfactorily done by clerks or para-medical workers. In this connexion, it would seem desirable to employ, whenever possible, health visitors in the screening procedures. It may also be possible to utilize medical students from Trivandrum.

There is need for as high a rate of acceptance of autopsy as possible, particularly in the case of stillborn infants and children dying at an early age.

12.5 Laboratory facilities required

It is difficult at this stage of the planning to foresee the demands for laboratory facilities ; however, the possibility that laboratory space and personnel will be required at some time in the evolution of the programme should not be overlooked. The availability of air transportation may suggest sending blood and other samples for examination to laboratories out of the area, at least for more complicated or extensive types of investigation.

12.6 Other requirements

The most obvious requirements of a non-personnel nature will be (1) adequate, independent land and water transport; (2) office accommodation ; and (3) access to data-handling machinery of a variety of types.

12.7 Institutional relationships

The Committee hoped that the active participation of the interested educational institutions would not only greatly add to the scientific resources available to the study, but at the same time substantially advance the educational interests of the institutions themselves.

13. Summary and Conclusions

1. There is an increasing interest in many parts of the world in the effects of radiation on man and his environment, but opportunities to study the genetic effects of the irradiation of human populations are limited. One such opportunity arises through the existence, at widely scattered points on the earth's surface, of areas with significantly increased amounts of background radiation. This report has attempted to review the general considerations which enter into the study of such areas, and to apply these general considerations to the steps that might be taken in organizing studies in one of the better known of these areas, namely, the Kerala area of India.

2. After a brief survey of the known areas of high-background radiation, the kind of information to be collected in such studies has been discussed. The decision as to what types of information are most appropriate depends upon many factors which will vary widely from population to population. Only rarely will it be feasible to base a study on a comparison of the frequency of appearance of specific mutant phenotypes in the irradiated and control populations. Much more frequently, reliance must be placed on a comparison of populations with respect to those characteristics which we assume reflect the cumulative effect of mutation at many loci, characteristics such as sex-ratio, life-span, fertility, etc.

3. It is suggested that it is convenient to consider such studies in terms of " levels " of information, the lowest levels being not only most readily collected and making the fewest demands on the time of specialized personnel, but also, in some instances, being indispensable to the acquisition of higher levels.

These levels are :

(*a*) accurate vital statistics ;

(*b*) growth and development data ;

(*c*) patterns of congenital defects ;

(*d*) clinical morbidity and mortality patterns ;

(*e*) laboratory studies ;

(*f*) necropsies.

4. The general statistical considerations which must enter into any such study as this have been reviewed. These are of two types : (*a*) considerations which enable conclusions to be reached concerning the possible biological significance of the study, and (*b*) considerations which will guide the analysis of the data.

5. The Committee wishes to emphasize the fact that properly designed and conducted studies on radiation genetics in such areas cannot fail to make significant contributions to many aspects of genetics and human biology. The Committee also draws attention to the role properly designed genetic studies may play in extending existing information concerning the somatic effects of continuous exposure to relatively high levels of background radiation.

6. With respect to a specific study in Kerala and the adjacent areas, the following points should be mentioned :

(*a*) There is a relatively stable population of approximately 80 000 persons living in well-defined areas in which the background radiation is, on the average, 10-15 times that normally encountered. The available evidence suggests continuous occupation of these areas by at least some of the ancestors of the present population for relatively many generations.

There is thus an opportunity to investigate not only the occurrence of induced mutations, but the fate of these mutations as regards visible effects on the populations in which they are being introduced.

(*b*) What appears to be a suitable control population is readily available.

(*c*) The first step towards the actual conduct of studies in these areas would appear to be a carefully conducted *ad hoc* census. The items to be included in such a census are outlined in section 11.1.3. This census would serve the dual purpose of defining accurately the area under study and of answering certain important questions concerning the comparability of the control populations.

(*d*) Although a considerable amount of information on the important question of dosimetry is available, more extended measurements aimed at producing the best estimate of the mean individual accumulated gonad dose at various ages are essential.

(*e*) Following the completion of the *ad hoc* census, a continuing effort at the collection of accurate demographic and vital statistics would appear to be the next step in the evolution of the programme.

(*f*) In the interests of better planning and to ensure maximum co-operation from the population, it is desirable to initiate pilot medical studies and services at the onset of the investigation. These pilot studies must be conducted in such a fashion as not to disturb the objectives of the *ad hoc* census.

(*g*) As soon as feasible, it would appear appropriate to perform some type of systematic, standardized medical examination on all, or an appropriately selected sample of, the inhabitants of the high-level and control areas.

(*h*) It seems unwise to specify further the details of an elaborate study when many of the factors necessary to intelligent decisions are still lacking.

7. The Committee regards it as rather improbable that the investigation of any of the high-background areas known today will, by itself, lead to the demonstration of significant genetic changes. The Committee is cognizant, however, of the desirability of obtaining meaningful data, imperfect though they may be, on the consequences of prolonged exposure to low doses of radiation. Such is the present status of our knowledge of the somatic and genetic effects of chronic low-level exposures that any proper investigation of areas of high natural radiation is certain to contribute to the fund of biological knowledge and the ultimate specification of the genetic risks accruing from increasing exposure to ionizing radiations.

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