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**News & Notes    \*\*    Abstracts**

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## **Procedures For Publication Of Conference Papers**

The Sub-Committee appointed by the Technical Committee of the Association have Lald down following procedures regarding publication of papers presented at the National Conference on TB and Chest Diseases :—

(1) Papers approved by the Technical Committee for presentation at the National Conference be published in the Proceedings of the Conference.

(2) Papers presented at the National Conference can be reproduced in full or part thereof in the Indian Journal of Tuberculosis and the author intimated of the same.

(3) Papers presented at the National Conference may be reproduced in full or part thereof in any other Journal after obtaining permission from the Secretary-General of the Association and the acknowledgement to be read as : “This paper was presented at the . . . National Conference on TB and Chest Diseases held at . . . and has been/is being published in the Proceedings of the Conference.”

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## PLANNING, CONDUCT AND EVALUATION OF RESEARCH STUDIES

An unusual observation and deductions therefrom for possible cause of such an observation is, generally, the mother of research. A real research worker will not rest content with this only. He will, thereafter, take suitable steps to solve problems arising out of such an observation. This is how man has delved into the depths of the unknown and collected figures and facts for the benefit of mankind.

Many epoch-making discoveries were made in the past by individuals. Because of rapid advances in medical and sister sciences, and development of specialities, individual effort is being replaced by that of a "team" in solving most of the problems. It has, however, to be conceded that the fountain of research is still the individual with a bent of mind for careful observation and deductions therefrom. To get the right answer or, in other words, to fulfil the objective of the study, the planning, conduct and evaluation of the findings should be entrusted to a suitable 'team' of experts.

Most often, specially for operational research, inclusion of a "Statistician" is of vital importance in a research team.

It is obvious that such a "team" must work like a well-oiled machine. For this purpose, all members of the team must clearly understand each other's views and stand-points. The problem to be investigated must be defined, expressed in an unambiguous language and should, preferably, remain clear of other issues. Terminologies to be used for accord must also be defined in clear and simple language. Planning of the study should take into account all possible sources of errors and biases with an effort to eliminate or diminish them. Many other factors may also have to be considered. The design of a study must, therefore, be built with great care in which every participant should have his say and share of responsibilities. All these spokes in the wheel of study must be in the realm of practicability, and should strengthen confidence in the final interpretations and conclusions.

The practice of seeking help of a "Statistician" at a late stage for interpretation of data and drawing conclusions is utterly wrong. The data

can be correctly interpreted only when the design of a study is adequate and information rightly recorded. Besides, and this is most important, the data must be interpreted with common sense in relation to the purpose and picture of the structure of the study. The Statistician must, therefore, be associated from the start to the finish of a study. He should be deeply involved in planning, check its conduct, agree to any interim modification of the plan necessitated by unforeseen conditions and finally have the largest say in the evaluation. This is true both for a planned and retrospective study.

India is largely involved in the field of operational research to develop a suitable tuberculosis control programme. Few well-equipped institutions may have the resources to plan such studies. This is hardly possible for others. At the same time, the subject of tuberculosis is such that data, restricted by uneven distribution of regions, may have many failings. To obviate this, well-planned and supervised co-operative studies, designed by a team of experts, appears to be the best method. It increases immensely the confidence not only in the conclusions but also their acceptability for the country's control programme.

Writing a paper on a study is also an art. The manner of presentation should differ in long and short publications and at Conferences. For the latter, tables etc. to be projected should not usually contain details but should be clean and highlight the important points only. In short, the presentation should take into account the consumers and allotted space or time.

The four papers on Statistics published in this issue of the Journal provide valuable guide-line in regard to utilisation of statistical methods in medical research.

## AWARD OF T.A.I. GOLD MEDAL

The Fourth Award of the Tuberculosis Association of India's Gold Medal for outstanding work in the Tuberculosis field was conferred on Dr. P. V. Benjamin at the time of the 24th National Conference on Tuberculosis and Chest Diseases held in Trivandrum in January 1969.



**Dr. P. V. Benjamin**

Born on 21st January, 1896, Dr. P.V. Benjamin graduated from Madras Medical College in Medicine in 1922. After taking his Diploma in Tuberculosis Diseases at Cardiff in 1930-31 he toured extensively the Scandinavian countries, Europe, Germany, the U.K. and the U.S.A. to study the anti-tuberculosis work in those countries. He was attached to the Union Mission TB Sanatorium from 1922 as one of its senior doctors and was its Medical Superintendent for over ten years. He became Medical Commissioner of the Association in 1941 and in 1944 was designated as its Technical Adviser. In 1948 he was appointed as TB Adviser to the Government of India and continued functioning as Technical Adviser to the Association. He retired from Government service in October, 1962 but continued as Technical Adviser to the Association upto the 1st of July, 1964.

Dr. Benjamin is an ardent champion of voluntary work and did his best to promote the work of the TB Association. He was member of the Technical Committee of the Association from its inception in 1948 upto 1964 and was President of the Ninth Tuberculosis Workers' Conference held in Lucknow in 1952. He was Editor of the Indian Journal of Tuberculosis from 1953 to 1964. He was responsible for introducing the TB Seals Sale Campaign in India, for developing the Mehrauli TB Hospital and for upgrading the New Delhi TB Clinic as a Training and Demonstration Centre. He was responsible for the introduc-

tion of BCG Vaccination in India. He persuaded the various Universities to institute Diploma Courses in Tuberculosis Diseases. He set up a separate Section for Tuberculosis in the Directorate General of Health Services. He advocated domicilliary treatment of patients and prepared suitable schemes for the purpose in the national development programme. He was responsible for the establishment of the National Tuberculosis Institute in Bangalore, the Chemotherapy Centre in Madras, the Tuberculosis Research Centre at Madanapalle and for starting TB Training and Demonstration Centres in different States. He initiated the National Sample Survey in 1956-57 and a number of research programmes.

Dr. Benjamin conducted in 1943 a Survey of sanatoria in India with a view to provide accommodation for TB patients in the Indian Army. As a member of the TB Sub-Committee of the Health Survey and Development Committee he submitted the Memorandum on tuberculosis. He was a member of the Health Panel of the Planning Commission. He was closely associated with the Indian Council of Medical Research. He contributed a Section on "Tuberculosis in the Tropics" in the book "Symposium on Tuberculosis" written by Prof. Heaf of Cardiff.

Dr. Benjamin is well-known among the international group of TB workers. He was a delegate to the first Empire TB Conference held in London in 1937 where he presented a paper on 'Indian People and the TB Problem'. He attended almost all International Conferences in TB subsequently. He was closely associated with the International Union and was a member of its Executive Body, Council and Technical and Programmes Committees for several years. He was President of the International Union during 1955-57 and presided over the XIVth International TB Conference held in New Delhi in January, 1957. He visited several countries in the East in connection with the formation of the Eastern Regional Committee of the International Union and was its President from 1957 to 1964. He was a member of the W.H.O. Expert Committee on Tuberculosis for a number of years and was consultant to the

W.H.O. Seminar on Tuberculosis held in Sydney in May, 1960. He represented India at the South East Asia Regional meeting of the W.H.O. held in Djakarta, Indonesia, in 1955. He advised the Nepal Government in regard to their anti-tuberculosis work. He has published over 100 papers on survey, research and various aspects of tuberculosis. He was made Honorary Life Member of the International Union Against Tuberculosis at its meeting in Amsterdam in 1967.

Dr. Benjamin is regarded as the 'Father' of the anti-tuberculosis movement in India and as an 'Elder Statesman' among international experts. He was awarded the Kaiser-I-Hind Gold Medal in 1945. He was awarded in 1955 TADMA SHRF by the President of India and the Sir Robert Philip Gold Medal by the N.A.P.T., London. In recognition of his outstanding services the Tuberculosis Association of India is honouring him with its Gold Medal-1969.

## PLANNING OF RESEARCH STUDIES\* (Some General Considerations)

S. S. NAIR

(From National Tuberculosis Institute, Bangalore)

### Need for a perspective on research

Research is a word which is commonly used now in many walks of life. But it is doubtful whether it has a commonly accepted meaning among medical research workers or even among the smaller group of tuberculosis and chest diseases workers. Some have their own pet idea of research and are indifferent to or even cynical about other forms of research. It is important to accept a general definition of research and to recognise that all types of research are valuable and also that their relative importance may change from time to time. The progress of research can be substantial and real only if research activities are guided with a proper perspective of such changes in the relative importance of the various types of research. A disproportionate emphasis on certain out-moded forms of research can prove to be very detrimental to speedy scientific developments. This dynamic approach necessarily implies that a small group of experienced research workers, with proper perspective of the trends and future needs of research should provide the necessary guidance and co-ordination to a band of research workers with appropriate attitude towards research.

### Attitude towards research

The importance of a proper attitude towards research has been emphasised by many eminent scientists. In 1949, Sir George Pickering, Regius Professor of Medicine in the University of Oxford stated that the attitude of mind "tends to be omniscient rather than admit ignorance, to encourage speculation not solidly backed by evidence, and to be indifferent to the proof or disproof of hypotheses. And, it is above all, to this habit of mind so inimical to scientific inquiry that the experimental method has found so small a place in clinical studies". It will be quite instructive for each one of us to ponder and judge for ourselves whether this statement, made 20 years back, still holds good, and if so to what extent. Can we at least have the satisfaction that it is no longer true for the majority of medical research workers in India. If not, there is room for considerable improvement in this respect and concerted efforts over the whole country may

\* Paper read at the 24th National Conference on TB of Chest Diseases held on Trivandrum in January 1969.

be necessary to find a speedy solution to this basic problem.

### What is research ?

Research has been defined by Bernard Ostle as an inquiry into *the nature of, the reasons for, and the consequences* of any particular set of circumstances—whether these circumstances are experimentally controlled or recorded just as they occur. To be of value, research must provide reproducible results which can be extended to more complicated and general situations, at least to a limited extent. Research has also to be considered as a continuous process involving the following stages:

1. Careful study of available data to formulate hypotheses to be tested in a new study,
2. Designing a proper experiment or study to test these new hypotheses,
3. Collection of data by careful experimentation or observation,
4. Testing the new hypotheses on the basis of the data collected, and
5. Careful study of observations which are not in agreement with accepted hypotheses and formulation of other hypotheses, if necessary.

Any research study could be expected to serve a dual purpose. Firstly, it provides data to test the hypotheses or answer the questions which prompted the study. Secondly, a careful study of the data could result in the formulation of new hypotheses to test which further studies are required. If the first purpose is not served it is bad planning and if the second is not done it is a failure to take advantage of all the information which has been collected. Sometimes, research workers are tempted to reject or ignore those observations which do not fit in with their hypotheses. This practice is not desirable. In fact, these unexpected observations are likely to provide golden opportunities for the research worker to get closer to the truth. Let us remember that it is the isolated light-house and not the cluster of houses that help the sailors to reach their destination. The need for and importance of an objective scrutiny of unexpected observations is often not clearly understood.

It is also instructive to remember that there are two clear trends in research, which are somewhat contradictory. While there is a tendency for extreme specialization on the part of individual research workers, most research problems are such that many disciplines and fields of specialization have to collaborate for finding the best solutions to the problem. These two trends imply that the individual research worker has to understand and maintain a proper balance between specialized research and collaboration in research on multidisciplinary team basis. Thus, we should not (and probably could not) any longer refrain from identifying ourselves as an army of research workers, who have to collaborate sooner or later so that quicker progress can be obtained in both quality and quantity of research work. Such an army of research workers should have a proper understanding of the planning of research studies and should be amenable to a self-imposed research discipline which alone can ensure research work of uniformly good quality.

### Types of studies

Research studies could be broadly classified in a number of ways. One type of classification is into prospective and retrospective studies. The latter cannot generally provide such clear cut and reliable answers as the former, and might even be misleading if not cautiously used. Yet, these have an important place. For example, double events such as congenital defects following an attack of some diseases can be studied only when these occur by chance from time to time and cannot be planned. Similarly, we cannot submit mankind to a large scale smoking experiment for 20 to 30 years to measure the relative frequencies of cancer of the lung among smokers and non-smokers. Retrospective studies provide valuable information in such instances. This category of studies can also be used to formulate hypotheses for further prospective studies.

Research studies could also be grouped according to the fields or aspects they cover viz.,

1. basic research,
2. controlled trials (e.g., for testing efficacy of drugs or vaccines),
3. epidemiological and sociological surveys,
4. studies to define 'normals' to judge point or level for 'some abnormality

(e.g., normal blood pressure, blood sugar level etc.)

5. studies to develop diagnostic techniques by measurement of sensitivity, specificity and overall accuracy, and
6. operations research to achieve maximum efficiency in the application of existing knowledge and skill.

The first type has been and shall always be of fundamental importance. Based on the foundations so provided, types 2 to 5 evolve the technical knowledge necessary to achieve the cure and control of diseases. Type 6 deals with all aspects of conducting or operating a system in its natural environment and recognises the fact that technical knowledge is only one of the components of the system. In these days, when the efficient management of any organisation or programme, be it big or small, depends not only on the level of technical know-how but also more and more on many operational factors, the importance of operations research is being increasingly recognised in many fields. It is only a matter of time that these concepts will find easy acceptance among medical research workers also. The earlier this trend is visualised and acted upon, the more advanced and substantial can be our contribution to the speedier development of medicine and public health.

A third manner of grouping research studies is on the basis of whether the results obtained directly contribute to a practical course of action or mainly contribute to knowledge only. Whatever the method of grouping, it is important to remember that many types of research studies are possible and that the type of study to be chosen will depend on the objectives of the study.

### Defining the Objectives

A clear formulation of the objectives is the first step in planning of research studies. This is also the most crucial step because every subsequent step in the study is dependent on the objectives. For instance, the composition of the study groups and the accuracy required for the measurements or observations are dependent on the objectives of the study. Sometimes slight variations in the objectives may have to be accompanied by vast changes in the design of the study and may even require the choice of another type of study altogether. For instance, a comparison of the allergy inducing capacity of two BCG vaccines can best be studied by a simple controlled trial with a trained team of field workers. Let

the objective be changed to comparison of allergy inducing capacity of two BCG vaccines under field conditions. With the addition of the last three words to the objective, a number of complicating factors such as effect of variations between teams of technicians, differential effect of storage on the two vaccines etc., crop up. The problem can then be studied only with the help of a considerably more complicated design and may even require a series of studies.

In defining the objective it is essential that the exact sense in which each term is used is known and thoroughly understood. It is also necessary that the objectives are stated as completely as possible and do not leave room for different interpretations regarding the context and scope for generalisation. If the study is to form the basis for a practical course of action, the expectations in this respect should also be clearly stated.

It would be a good working principle to formulate in advance, on the basis of available knowledge, as many hypotheses which can be studied with the available resources. Such an open-minded approach is the essence of good planning and prevents a dogmatic attitude. To quote Francis Bacon "If a man will begin with certainties he shall end in doubts, but if he will be content to begin with doubts he shall end in certainties". During the preliminary stage of formulating one's doubts or hypotheses it is important to ask oneself 'can this hypothesis be tested by an experiment and if so in what manner?' This will help a great deal in selecting out the hypotheses to be tested by the proposed study and thereby lead to a clear enunciation of the objectives of the proposed study.

### Scope of the Study

Closely related to the objectives of the study is its scope. While the objectives define what we want to find out about a particular population, the scope is the extent to which the findings from this population can be generalised. For instance, the findings from a representative sample of patients attending an urban clinic can be strictly true only for patients attending that clinic, but can be generalised to patients at other similar urban clinics in that city or town and may be to such patients in other urban areas also. The extent to which such generalisation can be made depends upon how far the particular population studied is representative of the population for which the Results have to be generalised. Both objectives and scope of the study should be thoroughly discussed with the . statistician so that he could assist in selecting the type of study, the design

of the study and the size of the study population to be examined or observed. It is also important to explain to the statistician all the aspects which are relevant or may be even doubtfully relevant to the problem and the onus for this must rest with the research worker.

### Type of Study to be chosen

Once the objectives of the study are clearly formulated the choice of the best type of study becomes fairly obvious. However, practical considerations may restrict this choice. For instance, if making fresh observations in a planned manner is not practicable, only retrospective studies could be attempted even if a prospective study is considered to be more suitable. Similarly, limitations of resources may also limit the choice to the second best type of study. These restrictions might also involve a re-formulation of the objectives.

### Design of the Study and Allocation into Study Groups

The design of a study is the complete sequence of steps considered in advance to ensure that the appropriate data will be collected in a systematic and well defined manner so that an objective analysis of these data could lead to valid inferences about the problem under study. Design of the study should be the primary responsibility of the statistician.

The requirements of a good design are that:

1. The comparisons to be made should be, as far as possible, free from systematic error, bias and influence of the factors which cannot be separated, eg., if initial and follow-up X-ray pictures are read by different readers, the change in status cannot be ascertained correctly because reader differences also play a part and cannot be separated. Similarly any systematic error or bias affecting one group will also be merged with other differences between this group and the other groups studied.
2. The comparisons should be made sufficiently precisely and it must be possible to assess the uncertainty or lack of precision in the conclusions. To ensure this, it is necessary to, allocate the study population into different groups on the basis of the statistical principles of random sampling and estimation of error.

3. the conclusions should have as wide a range of validity as possible without decreasing their precision,
4. the experimental arrangement should be as simple as possible, and
5. there should be a reasonable balance between precision of the conclusions and the cost of the study. If the conclusions are not reasonably precise the study is almost useless, but aiming at an unnecessarily high degree of precision implies avoidable wastage. This is so, because, other conditions remaining the same, the precision of the comparisons between any two study groups increases or decreases as the number of persons studied in these groups increases or decreases.

In studies dealing with uncontrolled populations, it is essential that very high coverage of the study population should be obtained. If this is not possible the design should include collection of other relevant information regarding the non-respondents to find out whether they form a special group.

At the time of finalising the design of the study, it would be helpful if the outline of the type of tables (i.e., dummy tables) for analysis of data and the statistical tests of significance for proper interpretation of the data can be visualised. This helps in ensuring, before it is too late, that the study population and its allocation according to the design are suitable. Also, wastage, by collection of unnecessary details which will not be made use of later, can be avoided.

### **Preparatory Work**

The next important step is the preparation of forms and cards for recording of information during the field or laboratory work and of detailed work instructions to each category of staff concerned, on how to carry out each step of their work and record their observations. These cards and forms as well as the work instructions should be pre-tested during a pilot phase and finalised on the basis of this experience. If necessary, further training should be given to the staff before starting the actual study. It is important to ensure that the definitions and terms used are thoroughly understood and uniformly interpreted by each member of the staff concerned. Definitions can often be misinterpreted during actual observations and recording of data. Each interpretation is in effect a separate definition

and the data collected will therefore be based on differing definitions. This is particularly true when observations are recorded in a number of centres or over a long period of time.

### **Conduct of the Study**

During the course of the study, adequate supervision should be exercised to ensure that the work instructions are followed strictly. This has to be visualised at the planning stage itself and arrangements should be made to ensure regular flow of information to a statistical unit which can thoroughly scrutinise the data collected and report on departures from work instructions. This is particularly important in the early stages of the work and could prove very useful to the supervisor. This process of scrutiny of records and supervision should be continued throughout the study so that uniformly good quality of data can be collected. Choosing the best type of study and a proper design and absolute accuracy in analysis and interpretation of data will be of no use at all if the basic data are incorrect or unreliable in any way. It is not unusual to find that data are collected in a hotch-potch manner under the wrong impression that analysis can get something useful out of it, especially if a statistician can juggle with it.

### **Adequate Provision for Analysis and Interpretation**

At the time of planning a study, adequate provision should be made for analysis and interpretation of data. This is particularly important for larger studies. This aspect is often ignored till the study is completed and leads to considerable delay in preparation of the report. Even more important is the continuity of the staff from planning to reporting. The team of research workers (including the statistician) who have planned the study and lived with it will know the pros and cons of the material very intimately and they alone can do full justice to it at the reporting stage.

### **Need for Collaboration with the Statistician**

The foregoing paragraphs have also indicated the need for a close collaboration between the medical research worker and the statistician. It would be instructive to consider the current practices in this respect. A perusal of the current literature shows that there is an increasing "prevalence" of the statistical methods in scientific studies. But, unfortunately, to some extent at least, this is based, not on an understanding of the underlying reasons but on

the assumption that use of tables, graphs and mathematical formulae give more authenticity and respectability. It is not uncommon to find reports on some truly subjective studies which have thus been invested with a false show of objectivity. The lack of proper appreciation of the importance of statistical thinking and methods at various stages of a research study has similarly led to varying levels of collaboration with the statisticians. Sometimes such collaboration is considered as a formality to ensure financial resources or to bestow a stamp of acceptability. There are also instances of collaboration which are on a par with the following answer to the question, "Do you believe in ghosts?" "No, but I am afraid of them". The belief that statisticians deliberately make simple questions difficult is also not uncommon and could have retarded the growth of healthy collaboration between the doctors and statisticians. Successful collaboration demands that the statistician should learn all he can of the problem in question and the medical man should learn all he can about the statistical approach. Without substantial knowledge on both sides it might turn out to be, blind leading the blind. Those research workers who are reluctant to learn or apply the statistical approach may not have realised that a new language is a riddle before it is conquered but a power in the hand afterwards. In any case, it is important to remember that the time for consulting a statistician is before planning the study, during the planning, during interim review to ensure good quality of data and during the analysis and interpretation—in fact, he should be involved in all stages of the study whenever possible.

### **Need for Co-operative Studies**

The field of medical observation is complicated because of some inherent variations. No one doctor can treat sufficient number of cases in a short span of time and a large number of doctors may each treat a few cases. The cases themselves are far from being a homogeneous group. The research worker in the field of public health faces the further difficulty that he cannot set up and control his own experiment in his own laboratory or clinic. In such circumstances, both for clinical and public health research co-ordinated team work in the same area or spread over a number of areas is often necessary. In the absence of such co-operative studies the literature becomes full of claims, assertions and counter assertions each of them being correct in its own limited manner, like the four blind men describing the elephant. In a country like India, where conditions can vary to a large extent such co-

operative studies become all the more important. Important findings from a study in one part of the country could be generalised with more confidence, if similar studies are conducted under different realistic conditions. Such co-operative studies become all the more important in operations research because the practical conditions under which knowledge and skill are actually applied for the benefit of the community or nation introduce a number of key variables which have great influence on the outcome. Some factors considered to be technically important pale into insignificance in the light of some of these key variables.

### **Need for a Rigid Research Discipline**

The success of such co-operative studies would depend upon the participating units following a rigid research discipline. Even studies in one area only, will become more valuable if the quality of the research work becomes uniformly good and reliable. What is often not recognised is that a self-imposed research discipline is essential among research workers. The more rigid it is, more valid will be the conclusions and more comparable will be the findings of different studies. Whereas problems vary from area to area and population to population, the research discipline need not vary, as the basic concepts are fundamental and uniformly applicable. The reasons for the lack of self-imposed research discipline can, therefore, be only artificial or man-made.

### **Conclusion**

Some of the statistical principles which have to be kept in mind while planning research studies and the various steps that have to be gone through have been indicated earlier. It would be a very revealing experience to go through the research studies already undertaken or in progress and see how many of these satisfy these principles or have gone through the various steps listed. It is not unusual to find reports of research studies in which the questions or objectives are either not clearly formulated or are not stated at all. Sometimes, the type of studies chosen, the design, the study population and the analysis are not suited to provide valid answers to the questions formulated or the hypotheses to be tested. Lack of adequate arrangements for continuous supervision and scrutiny of methods of observation and recording is much more common than normally visualised. There are also instances which remind one of the saying that "statistics are used the way a drunkard uses a lamp post; for support rather than for light". The only practicable remedy for these situations is a self-imposed research discipline.

# PLANNING, CONDUCT AND EVALUATION OF CONTROLLED CLINICAL TRIALS\*

S. RADHAKRISHNA

(From Tuberculosis Chemotherapy Centre, Madras)

The controlled clinical trial is now a well-accepted method of measuring the relative efficacies of different therapeutic regimens for many diseases. Although its usefulness is widely appreciated, there is an insufficient awareness of the rationale and the methodology of the controlled clinical trial—that is, the reasons underlying it and the procedures involved in the execution. By taking examples from the field of pulmonary tuberculosis, the issues involved can be clearly set out.

### *Specification of regimen and priority in aims*

To evaluate the efficacy, toxicity and acceptability of an anti-tuberculosis regimen—for instance, isoniazid plus thioacetazone, it is necessary to start with very clear ideas of the dosage, the rhythm of administration and the exact duration of the regimen. Next comes specification of the order of priority in aims as there can be a clash of interests. For instance,

#### *1. Specification of Regimen and Priority in Aims*

Specify clearly
(a) dosage, rhythm and duration
(b) priority in aims
(1) Efficacy
(2) Toxicity
(3) Acceptability

if the main aim is to determine the efficacy of the drugs, it will obviously be necessary to employ procedures for detecting irregularities in drug-collection and drug-intake, and correcting them. Such action would, however, mean that pressure is applied on patients when they show evidence of non-acceptability, thereby making any assessment of the acceptability of the regimen rather artificial. This is a good illustration of the basic maxim that any study can have only one main aim.

#### *Choice of patients for study at the T.C.C., Madras*

For any generalisation to be possible from the results of a study, it is necessary to define

very clearly the type of patients to be admitted. To give an example, Slide 2 sets out the important criteria employed at the Tuberculosis Chemotherapy Centre, Madras.

#### *2. Choice of Patients for study at the T.C.C., Madras*

1. Aged 12 years or more
2. No previous chemotherapy
3. Bacteriologically confirmed pul. Tb.
4. Drug-sensitive organisms
5. Bonafide residents

It is important also to specify contra-indications for admission to the study—for example, patients with leprosy or diabetes, since their management would be rather complicated.

The next requirement is a control group of patients.

#### *Need for control*

Slide 3 gives some interesting examples of entirely inaccurate or highly misleading conclusions that one might draw in the absence of a control group of patients.

#### *3. Need for Control*

Relapse rate	Rx for 3 years	1% of 77
	Rx for 2 years	0% of 74
Giddiness	Strep. + 1NAH	35% of 78
	PAS + 1NAH	11% of 70

The first example refers to relapse rates in patients with bacteriologically quiescent tuberculosis. In patients who received chemotherapy for 3 years, the total relapse rate in the third, fourth and fifth years was only 1%. This low proportion could have led to the recommendation that 3 years of chemotherapy is absolutely necessary to keep the relapse rate low. (Indeed, similar recommendations have been made in the literature, in the absence of controls). Such

\* This paper was presented as a *lecture* at the 24th National Conference on TB and Chest Diseases, held in Trivandrum in Jan. 1969

a recommendation is, however, totally unwarranted since, in the patients who received only 2 years of chemotherapy, the relapse rate was 0%.

The next example is a less extreme one, and pertains to toxicity. In a group of patients treated with a twice-weekly regimen of streptomycin plus isoniazid, 35% complained of giddiness on at least one occasion during the year of chemotherapy. However, 11 % of the control group (who received a standard regimen of PAS plus isoniazid) also complained of giddiness. Thus, in the absence of the control group, we would have acquired an exaggerated picture of streptomycin toxicity.

Examples like this are plentiful. For instance, in the treatment of tuberculosis, conclusions about the value of gold therapy, value of hospitalization and role of diet have been drawn and, in the case of the latter two, are still being drawn without having a control group of patients.

These examples will have convinced you of the necessity for having a control group of patients. In the present context, the control might be a regimen that is already in use at your clinic, for instance, a standard regimen of isoniazid plus PAS.

*Need for concurrency*

4. *Need for Concurrency*

Factors that could vary
1. Disease condition of patients
2. Co-operation of patients
3. Clinic supervision
4. Laboratory standards

Next, it is essential that the control should be a concurrent one. Comparisons with a non-concurrent control—that is, retrospective comparisons—are usually dangerous, as there are many factors that could vary from one point in time to another. For instance, the disease condition of the patients admitted to treatment might be different in different years, on account of changes in diagnostic measures or influence of mass propaganda campaigns. The co-operation displayed by the patients might also vary from one year to another, possibly due to socio-economic causes. Thirdly, the intensity of examination and the overall quality of the clinic supervision might be different, especially if there have been changes in the personnel. A similar problem can arise with the laboratory

standards for smears, cultures, sensitivity tests and urine tests. Obviously, the only way out of these dangers is to have a control group that is concurrent.

*Number of patients to be admitted*

Next, let us consider the question which is most frequently posed to the statistician, namely, "How many patients must I admit to the study to obtain a statistically valid result?" Unfortunately, the short answer to this question is that there is no such magic number. However, if the clinician can indicate to the statistician the approximate efficacy of the control regimen and, furthermore, state what difference from the control regimen he would regard as having practical importance, the statistician can then tell them approximately how many patients should be admitted.

To take an example, the clinician might be interested in the new regimen only if it is 20% more effective than the control regimen, which from previous experience is known to have an efficacy of 75%. In this case—that is, an efficacy of 75% for the control and 95% for the new regimen, approximately 70 patients will have to be admitted to the study (that is, 35 in each series) to demonstrate statistical significance. If, however, the clinician wishes to

5. *Number of Patients to be Admitted*

Control regimen	New regimen	No. of patients to be admitted
75%	95%	70
75%	90%	130
75%	85%	290
75%	80%	1150

detect a smaller degree of superiority, say 15% (that is, an efficacy of 90% for the new regimen), the number required will be 130. The corresponding number for a 10% superiority will be 290, and for a 5% superiority 1150. Thus, the smaller the difference to be detected, the larger will be the number of patients required. It must be noted that the number required for statistical significance will depend not only on the size of the difference to be detected, but also on the absolute levels of efficacy of the two regimens.

It is worth stressing at this stage that statistical significance need not be the sole criterion

for determining the number of patients to be admitted. Very often, we are just as interested in obtaining as precise an estimate as possible of the efficacy of the new regimen. Obviously, the larger the number of patients admitted, the more precise will be the estimate. For instance, if the efficacy was found to be 80% in a sample of 100 patients, it may be stated, with 95% confidence, that the true efficacy lies within  $80 \pm 8\%$ . If, however, the efficacy of 80% had been observed in a larger sample of patients, say 400, the limits will naturally be narrower, namely,  $80 \pm 4\%$ .

Summing up, the decision regarding the number to be admitted must be based on objective considerations like statistical significance and high precision. Practical considerations like availability of patients, drugs and facilities are no doubt important but should always be regarded as secondary.

#### *Mode of deciding the regimen for individual patients*

Next comes the mode of deciding the treatment regimen for individual patients. In a controlled clinical trial, the mode of deciding the regimen for any individual patient must not only be free of bias, but also appear to be free of bias. One can readily see the danger in entrusting the choice of the regimen for individual patients to the clinician. To take a simple

#### *6. Mode of deciding the Regimen for individual Patients*

1. Clinician's choice
2. Alternation
3. Random allocation from sealed envelopes

example, if patients were to be treated at home or in sanatorium at the clinician's discretion (which might be, in some instances, influenced by the patient's wishes), it is almost certain that the iller patients would tend to be admitted to sanatorium while the less ill patients would be treated at home.

Another highly undesirable procedure is the method of alternation, whereby the first patient is prescribed regimen A, the second regimen B, the third regimen A, the fourth regimen B, and so on. A variant of this is to admit all patients on odd days to the regimen A and those on even days to the regimen B. Such procedures are, however, capable of bias because the order in which patients are admitted to a study can be manipulated without much difficulty. For instance, in a study of anticoagulant therapy

in myocardial infarction (quoted by Truelove), the system of alternation resulted in 580 treated patients and only 442 control patients, a difference that could have occurred by chance in only 1 of 5,000 occasions.

The best protection against all accusations of bias is random allocation from sealed envelopes. This procedure may be regarded as the equivalent of tossing a coin. In practice, it consists of preparing a treatment regimen list for successive patients based on random numbers that are available in statistical tables and incorporating it into sealed envelopes. Each sealed envelope must have written on its exterior the name of the study, and a sequential serial number. Inside each envelope, there should be a slip of paper giving the name of the study, the sequential serial number and the regimen for the patient. When a patient is found suitable for admission to the study, his treatment regimen is to be determined by tearing open the next in the series of sealed envelopes.

#### *Purpose of random allocation*

The purpose of random allocation is to avoid personal preferences in the choice of treatment for individual patients. It has to be emphasised that these personal preferences can be conscious or, more often, sub-conscious.

#### *7. Purpose of random allocation*

1. To avoid personal preferences, conscious or sub-conscious
2. To construct two groups similar in all aspects
  - (a) known and measurable (stratification)
  - (b) known but immeasurable
  - (c) unknown

Failure to recognise that there is such a thing as sub-conscious bias has often led investigators to regard random allocation as a slur on their personal honesty.

The great advantage of random allocation is that it is highly likely to result in the construction of 2 groups which are similar in *all* aspects—known and measurable, known but immeasurable or not measured, as well as the unknown. In the case of known and measurable characteristics that have prognostic importance, a further precaution would be to stratify the patients into 2 or more groups—e.g. non-cavitated and cavitated—and undertake the allocation from separate series of sealed envelopes, one for

each group. In the present example, this procedure will ensure that the two series have identical proportions of cavitated patients.

*Similarity in subsequent management*

Next, it is important to ensure similarity in the subsequent management of the patients in the 2 series. For this, it is necessary to set out in advance (1) the intensity of examination during treatment—clinical, x-ray, sputum etc., (2) the nature and frequency of checks on drug-

8. *Similarity in subsequent management*

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| <ol style="list-style-type: none"> <li>1. Intensity of exam.—clinical, x-ray, sputum etc.</li> <li>2. Checks on drug-regularity</li> <li>3. Defaulter action</li> <li>4. Observance of toxic symptoms</li> <li>5. Criteria for withdrawal from study</li> </ol> |
|---|

regularity, (3) procedures for dealing with defaulters, and (4) procedures for the recording of symptoms of toxicity. Finally, and most important, the circumstances under which a patient may be withdrawn from the study must be stated very clearly. For instance, the criteria could be serious radiographic or clinical deterioration in the presence of a positive sputum of major drug-toxicity. It must be emphasised that all these procedures must be implemented alike for all patients, regardless of the treatment regimen.

*Conduct of the study*

All that has been said so far relates to the planning of a controlled clinical trial. When the plan is fully evolved, a protocol should be written up which contains all these points, and made available to all participating physicians. The protocol should be treated as a sacrosanct document, and scrupulously observed in every

9. *Conduct of the study*

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| <ol style="list-style-type: none"> <li>1. Strict adherence to protocol                     <ul style="list-style-type: none"> <li>Reminder systems</li> <li>Deficiency-detecting systems</li> </ul> </li> <li>2. Design of forms and analysis cards</li> <li>3. Periodic abstraction of information</li> <li>4. Avoidance of bias in lab. investigations</li> <li>5. Quality control—lab. tests, drugs</li> </ol> |
|---|

detail—that is to say, no deviations can be made to suit the needs of individual patients or individual clinicians.

To facilitate strict adherence to the protocol, it is useful to have the important aspects (e.g. criteria for eligibility to study, intensity of the x-ray and sputum examinations, weight-dosage schedules) abstracted on to separate sheets of paper that are readily available to the clinicians and nurses ; also, diaries for reminding clinic staff of ensuing examinations should be kept. These are what can be termed as reminder systems. Despite these, deficiencies can occur ; it is therefore necessary to have systems for detecting deficiencies and rectifying them before it is too late.

Well-designed forms and analysis cards make analyses easy ; therefore much time must be spent on them at the design stage. Also, information collected should be abstracted periodically on to analysis cards. This will not only facilitate interim analysis, but also highlight deficiencies in the forms, cards and recording systems, which can then be rectified.

As bias can creep in to laboratory investigations, it is important to devise systems in which there is not even scope for bias. For instance, when smears are examined, or cultures or sensitivity tests read, or urine tests undertaken, it should be arranged that the laboratory technicians are unaware of the source of individual specimens.

Finally, it is essential to have quality control for laboratory tests and for drugs that are in use in the study. At the Tuberculosis Chemotherapy Centre, we keep track of the standards in the laboratory investigations by slipping in controls without prior warning and by periodic reviews of the incidence of contamination and smear-positive culture-negative results. As regards drugs, assays are undertaken routinely on arrival, and if necessary at periodic intervals thereafter.

*Evaluation of results*

Even in the case of well-planned and well-

10. *Evaluation of results*

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| <ol style="list-style-type: none"> <li>1. Be wary in excluding patients from analyses</li> <li>2. Check for similarity between series in                     <ol style="list-style-type: none"> <li>(a) initial condition</li> <li>(b) intensity of examination during treatment</li> </ol> </li> <li>3. Objective methods to ensure bias-free comparisons                     <ol style="list-style-type: none"> <li>(a) Independent assessor for x-ray reading</li> <li>(b) Clear definitions of fav. and unfav. response</li> </ol> </li> </ol> |
|--|

conducted studies, great care has to be taken in the evaluation of the results. One common error is the exclusion of patients from final analyses. Sometimes, the reasons are obviously unrelated to the treatment regimen; in such cases, it is sufficient to establish that the exclusions have occurred to a similar extent in both series. However, we have had examples at previous conferences where deaths from tuberculosis were conveniently excluded and cheerfully optimistic conclusions drawn from the findings in the survivors. Such procedures must be deplored strongly. The rule should be to describe the progress of all patients admitted to the study who belong to the population defined earlier (Slide 2).

Although random allocation can be expected to yield 2 series which are very similar in their initial condition, nevertheless, analyses should be undertaken to check that the 2 series were in fact similar on admission. Also, analyses should be undertaken to check that the actual intensity of examination during treatment was the same.

Finally, for assessing x-ray progress, it is important to obtain the services of an *independent* assessor who is not connected with the day-to-day management of the patients. Fur-

ther, the x-rays should be fed to the assessor in strict sequence of the patient serial number, which is by design a random sequence. Definitions of favourable and unfavourable response must be clear-cut, and applied alike to all the patients regardless of the treatment regimen. In other words, classifying patients as having a favourable or unfavourable response on an individual basis without laying down strict definitions is a highly objectionable procedure.

No evaluation can be complete without tests of statistical significance. However, the results of these tests must not be regarded as giving proof of existence or proof of non-existence of a difference. Thus, when we say that a difference is statistically significant, all that we mean is that the likelihood of it being a fluke observation less than 5%.

I would like to stress that planning, conduct and evaluation are not three water-tight compartments that can be dealt with independently by different people or different committees. At least one individual, preferably the chief investigator, must be deeply involved in all three stages, and all the other participants must understand and appreciate the rudiments of controlled experimentation, if the outcome of such efforts is to be valuable.

## PLANNING AND CONDUCT OF EPIDEMIOLOGICAL SURVEYS\*

G. S. ACHARYULU

(From Madanapalle Tuberculosis Research Unit, Madanapalle)

Pulmonary Tuberculosis is the most common form among the different forms of tuberculosis. The main indices useful in the epidemiological study of this disease are the prevalence and incidence rates of (i) persons infected with tubercle bacilli, (ii) persons excreting tubercle bacilli and (iii) suspect cases of tuberculosis (diagnosis not confirmed bacteriologically). With the occurrence of primary drug-resistant cases, knowledge of the prevalence and incidence of such cases has attained considerable importance.

There are two types of epidemiological surveys, prevalence surveys and longitudinal surveys. In prevalence surveys, the observations refer to a specific point in time. In longitudinal surveys, the observations are repeated at different points in time. Both prevalence and incidence rates can be estimated from these surveys. They are useful for making future projections of the tuberculosis problem and in evaluating the effects of different tuberculosis control programme.

Longitudinal surveys can be classified as experimental surveys and non-experimental surveys. The objective in experimental survey is to assess the value of or to compare the effects of different T.B. control programmes. In non-experimental surveys, no such assessments or comparisons are contemplated.

### Considerations in Planning the Surveys

The first step in planning an epidemiological survey is to define the objectives of the survey. This involves the specification of the purpose of the survey and the epidemiological indices which are to be estimated, and how the survey results are going to be made use of. On the basis of these indices it will be determined whether the survey should be a prevalence or a longitudinal type.

In experimental survey, the selection of the individuals into the study depends upon the type of population to which the experimental results are to be later applied. There are two situations : the first is, the population is supposed or known to possess certain characteristics which will interact, favourably or unfavourably, with the T.B. control measures, which are to be compared in the experiments ; the second is when there is no knowledge about any such

characteristics. In the latter situation, a sample reasonably representative of the population is selected according to practical convenience for undertaking the survey. In the former situation, the population will have to be divided into a number of strata and a representative sample will have to be selected from each stratum. An example of such a situation is provided by the presence or absence or non-specific sensitivity in the population in a study designed to investigate the protective effect of BCG Vaccination, as there is reason to believe that non-specific sensitivity offers some protection against tuberculosis.

Special problems which are to be considered in planning experimental surveys are :

- (i) incorporation of suitable 'controls',
- (ii) method of randomization and
- (iii) determination of the size of the experimental population.

In situations, when there is doubt regarding the effects of T.B. control measures or when the interest is in evaluating their effects, 'controls' must always be introduced in the experiment. If, on the other hand, there is no doubt regarding the effects of control measures and the interest is only in comparing the effects of different control measures, there is no necessity for 'controls'. If valid comparisons are to be made, the experimental units (an experimental unit consists of a single individual or any well defined group of individuals) should be randomly allocated to the different programmes. There are many methods of randomization and they make use of the knowledge, if available, of the inherent variability of the experimental material which is relevant to the investigation. The purpose of these methods is to increase the efficiency of the experiments by reducing the experimental error. The factors to be considered in the choice of a proper method of randomization are :

- (i) the types of control programmes to be compared,
- (ii) available knowledge of the inherent variability of the experimental material and
- (iii) practical considerations in the conduct of the survey such as actual process of randomization etc.

\* Paper read at the 24th National Conference on TB and Chest Diseases held in Trivandrum in January 1969.

Size of the experimental population will be determined by making use of the estimates of of experimental errors obtained from previous surveys.

There are two methods of undertaking prevalence surveys or non-experimental surveys ; complete survey method and sample survey method. The objective in both the methods will be to obtain knowledge of the distributions, aggregate or mean values of one or more characteristics of a well defined population. In complete survey method, observations are made for every individual in the total population, whereas, in sample survey method, observations are confined to a certain number of individuals in the population. On the basis of the selection of the individuals, samples can be divided into random and judgement samples. In random samples the individuals are selected according to the laws of probability while, in judgement samples, selections are not done according to these laws. The National Tuberculosis Sample Survey, conducted during 1955-'58, under the auspices of the Indian Council of Medical Research, is an example of random sample survey. The European Tuberculin Survey undertaken during 1965-'66 under the auspices of the International Union Against Tuberculosis and the First Drug-resistance Survey (1964-'65) conducted under the auspices of the Indian Council of Medical Research are two examples wherein judgement samples have been made use of.

The random sampling method makes it possible not only to estimate the population characteristics but also to estimate the errors involved in those estimates. This method will ensure that the samples will be representative of the population. On the contrary, there is no guarantee that the judgement samples will be representative of the population. Further, the errors involved in the estimates of the population characteristics cannot be estimated from judgement samples. Another disadvantage is, that it will not be possible to make valid comparisons of the estimates obtained from one judgement sample with those obtained from another. In view of these considerations, random sample surveys are always to be preferred. Judgement samples should be made use of only if it is not possible, owing to practical difficulties, to undertake random sample surveys.

With regard to the choice between random sample surveys (hereafter referred to as sample survey) and complete surveys, sample surveys are always to be preferred as they have several advantages over complete surveys. These are :

- (i) reduction in the cost of the survey,
- (ii) the speed with which the estimates can be obtained and
- (iii) a greater accuracy in the results.

Greater accuracy will be obtained as it will be possible to control the various sources of errors in collecting the data by employing technically trained and experienced personnel, when the survey is conducted on a limited scale.

The undertaking of sample survey requires:

- (i) the construction of a sampling frame,
- (ii) the choice of a sampling design and
- (iii) the fixation of the sample size.

The sampling frame consists of a list of sampling units in the total population without omission and/or duplication and this is essential for drawing random samples. The sampling unit may consist of an individual or all members in the household or a group of households in a contiguous area or any other well defined group. The sampling design stipulates the method of drawing the sampling units into random sample. For the same sample size, certain sampling designs will be more efficient than others, efficient in the sense of containing comparatively less sampling error. Although it is possible to minimize the sampling errors by choosing efficient sampling designs and suitably increasing the sample size, in practice, the decision regarding the sampling design will have to be taken on the basis of the sampling frame that is available and mainly in view of the operational convenience of the field work. The size of the sample will be fixed by the consideration of the cost of the survey and the margin of error allowed in the estimates.

### **Types of Data collected**

Specific data to be collected in any particular survey will be decided by the specification of the layout of the final statistical tables required from the survey. The types of data that are generally collected in epidemiological surveys relate to (i) census, (ii) tuberculin tests, (iii) X-ray examinations, (iv) bacteriological examinations, and (v) anti-tuberculosis measures. A discussion of the considerations in collecting some of these data may be relevant here.

### **Tuberculin Tests**

Although the importance of this test in measuring the prevalence and incidence of infection is well known, its value is restricted

by the use of BCG Vaccination. Hence, this factor, that is, the extent to which the population concerned was covered by BCG Vaccination is to be considered before deciding to use this test for measuring the epidemiological indices.

### X-ray examinations

In countries like India, children in the younger age groups constitute a considerable proportion of the total population. In view of the low prevalence and incidence of the disease among children, it is sometimes desirable to exclude them from these examinations. Such a procedure will reduce the work-load considerably and at the same time the resulting loss in precision of the estimates will be negligible. Regarding the interpretation of X-ray films, a suitable code to meet the specific requirements of the survey will have to be devised, as no internationally accepted code\* has so far been evolved for this purpose. Two independent readers are considered essential.

### Considerations in the conduct of the Survey

For the success of the survey, it is essential to have well trained and experienced personnel. When such personnel are not available, recruitment and training programmes will have to be undertaken well in advance. The various cards and forms to be used for collecting the data should be designed. A detailed protocol for the conduct of the survey should be prepared. This protocol should:

- (i) Specify the purposes and objectives of the survey;
- (ii) define the populations to be surveyed;
- (iii) describe the various methods of examinations to be conducted along with the criteria of classifications to be adopted;
- (iv) define the concepts to be used such as case of tuberculosis etc.;
- (v) contain detailed instructions to the staff working in different sections such

Efforts are being made by a specially appointed international committee (The Ad Hoc Committee for the study of Classifications and Terminology in Tuberculosis under the auspices of IUAT in cooperation with WHO), to evolve a code for interpretation which will be acceptable internationally and which will minimize the errors of interpretation.

as census taking, tuberculin testing etc.

The instructions to the field staff should be unambiguous and should contain typical illustrations. If necessary, a pilot survey may be undertaken. Such a survey will be useful (i) in the development of the field procedures, (ii) for testing the suitability of the various cards and forms designed and (iii) in giving training to the field staff.

An important aspect, particularly in the conduct of experimental surveys, must be mentioned here. This is to ensure that groups of individuals allocated to different control measures to be compared are treated alike throughout the survey with regard to the admission of the individuals into the groups, intensity of the diagnostic examinations and other factors except the actual control measures. How any such factor can introduce bias into the study may be illustrated by an example. In a BCG Trial, if places injections are not given to 'controls', it will not be possible to identify the group among the controls corresponding to the group of persons who refused BCG Vaccination. Another important aspect is that the identity of the control measures given to an individual should not be revealed either to him or to those who will have to assess the effects of control measures.

### Sources of Errors and Measures of Control:

In order to get valid and reliable estimates it is essential to minimize the errors which arise from several sources. These are broadly divided into sampling and non-sampling errors. Sampling errors occur only in sample surveys, whereas non-sampling errors occur both in sample and complete surveys. While the sampling error, as mentioned earlier, can be kept within predetermined limits by suitable measures, it will not generally be possible to identify all the sources of non-sampling errors and to estimate the extent to which they affect the final estimates.

Non-sampling errors arise on account of several factors and some of them are discussed below :

1. *Failure to examine the complete study population* : This is called the error due to non-response. One method suggested to obtain unbiased estimates of the population characteristics is to examine a random sample of persons who failed to report for the examinations earlier. This procedure will not be practicable in many situations. The other way of reducing this error is to minimize the percen-

tage of non-response by intensive efforts and to note down the reasons for non-response, so that an analysis can be made later to give an idea as to how the estimates are going to be affected.

2. *Biases* : There are two types of biases, systematic and unsystematic. The occasional failure to detect every bacillary case with single spot sputum specimen is an example of systematic bias. Such a procedure will lead to consistent under-estimation of the number of bacillary cases. The extent of under-estimation can be ascertained by conducting special studies or from the results of such studies made elsewhere. If the resources permit, this error can be reduced by better methods of sputum collection.

The effect of unsystematic bias is sometimes over-estimation and some times under-estimation. The unconscious preference for round numbers, generally observed in reading the tuberculin reactions and in reporting the ages, may be given as examples of unsystematic biases. The effects of these errors can be reduced to some extent, by suitably grouping the observations in preparing the frequency distribution when the data are tabulated.

3. *Errors in classification* : Generally, tuberculin positive reactors who are supposed to have been infected with tubercle bacilli are denoted to be those whose reactions exceed a certain size, for example 6 mm. or 8 mm. The dividing point between negative and positive reactors varies from one study to another and maybe anywhere between 6 to 15 mm. This type of definition is known to involve two types of errors, viz., inclusion of persons who have been actually infected with tubercle bacilli and exclusion of persons who have been actually infected with tubercle bacilli. The magnitude of these two types of errors depends upon the magnitude of the prevalence of non-specific sensitivity in the community. As long as the same definition is

used for this purpose, provided that other conditions are the same, comparison of estimates from one group with another will be valid. But, when the interest is in estimating the absolute value of the magnitude of infection with tubercle bacilli, efforts should be made to evolve an objective criterion for this purpose.

4. *Errors in data processing and tabulation*: These errors can be reduced by giving clear instructions, by employing well trained staff and by exercising constant supervision over them.

To sum up, the first step in planning a survey is to provide a clear and unambiguous statement of its purposes and objectives. Planning requires consideration of all important aspects of the survey, many of which are inter-dependent. The application of statistical methods is essential to get valid and reliable estimates and for making valid comparisons. Recognition of the types of errors which might occur in survey will not only lead to better planning and execution of the survey, but also to better understanding of the reliability of the estimates obtained from the survey.

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## ANALYSIS AND PRESENTATION OF DATA\*

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Assuming that a clinical trial, laboratory experiment, or epidemiological survey has been concluded and a mass of reliable data collected, there arises the question of analysis, interpretation and presentation. The vast quantity of information has to be numerically summarised and logically tenable conclusions drawn therefrom. The statistical techniques for dealing with data are determined largely by the plan of the study and the nature of the information collected. Analysis, in the main, is a job for the statistician and, as a rule, doctors and medical research workers need not aim at mastering the statistical methods applicable to different situations. However, an understanding of the general principles does help in the systematic compilation of the right type of data, in intelligent discussion with those who are mainly concerned with the statistical evaluation and in interpreting the final results. Indeed, it is only a continuation of the process, starting at the planning stage, whereby the medical research workers and statisticians learn to understand each other's language and arrive at a common basis for discussion.

It would be useful to start at the point where data are being collected and compiled. Except for large scale surveys, it is not really essential in most cases to resort to mechanical sorting and tabulation. Indeed, for studies involving a few hundred cases it is sometimes more advantageous to have either individual cards or even simple lists. The latter, preferably prepared in code, and incorporating all information, are in fact to be particularly recommended for small scale studies, since they permit an intimate acquaintance with the data, suggesting possible relationships between various characteristics and, in general, indicating the lines along which data should be analysed.

The form in which these entries are to be made itself needs to be carefully designed, special attention being paid to such matters of detail as units to be used, grouping of data and and above all to comprehensiveness. Simplicity, precision and legibility and other criteria which should be kept in mind.

The importance of associating the statistician with any research project from the very start has already been stressed. Data collected without any plan or with a defective plan may not lead to any worthwhile conclusions. Tests of significance and statistical analysis are only

valid if experiments, surveys etc. have been properly designed and all the rules observed. The most important are the ones concerned with random allocation and the elimination of bias; and with advance planning they are not difficult to comply with.

Statistical data usually are affected by a multiplicity of causes and this is more so in the case of biological data. For drawing valid conclusions from data influenced to such a marked degree by variation and chance, there exist powerful statistical tools. These are based on laws of probability and that is why conclusions drawn thereby, though not applicable to individuals, are true over large numbers of individuals. A special advantage of the statistical technique is that it furnishes estimates of the precision of the results obtained.

It would be obviously impossible within the short space of this paper to describe or even outline briefly the various forms of statistical treatment of data pertinent to different situations. As already stated, these are to a large extent determined by the nature of the studies. I would therefore content myself with a few general remarks.

Interpretation of biostatistical data is not merely a question of applying certain mathematical formulae and obtaining a result. Even more important than these are an exercise of one's logical and critical faculties. Medical journals are replete with instances where the wildest conclusions have been drawn by applying statistical techniques contrary to the dictates of commonsense and elementary logic. Even such apparently simple things as percentages, prevalence and attack rates can be dangerous in the hands of persons not accustomed to look at figures in a critical way. Special care needs to be exercised when conclusions are being drawn on the basis of a comparison between two groups. Unless it is ensured that the groups are similar in all respects, except the one under study, conclusions will not be valid. In many cases, the methods of random allocation would have taken care of such differences. In others one may have to resort to 'standardisation' to nullify the effect of inequalities in important respects.

Tests of significance are so widely used by statisticians and so often misunderstood by others that it is probably useful to say a word about these. As an example, let us consider a simple clinical trial in which a group of 100 patients has been divided at random into two

\*Paper read at the 24th National Conference on TB & Chest Diseases held in Trivandrum in Jan. 1969.

sub-groups, those in the first group getting drug regimen A and those in the other, drug regimen B. Assume further that at the end of a certain period, sputum conversion rates of 70% and 80% have been observed in the two respective groups. How are we to know whether the observed difference represents a real superiority of regimen B over regimen A or is merely due to chance? This is done by using a test of significance. To start with, we set up what is known as the 'null hypothesis'. In our particular example, for instance, we begin by assuming that the two drug regimens do not in fact differ in respect of sputum conversion. We then calculate the mathematical probability of getting a difference at least as big as the one observed if the 'null hypothesis' was correct. If this probability is sufficiently low, say 5% or less, we reject the null hypothesis and conclude that the observed difference is in fact real. It must however be remembered that, based on the laws of probability as it is, the test of significance cannot be said to have 'proved' the existence of a real difference. All it says is that the differences are very unlikely to have arisen by chance. Likewise, a 'not significant' decision does not 'prove' the absence of any real difference; it only means that the observed difference could well arise by chance alone. Incidentally, it is also possible for a difference to be statistically significant, and yet unimportant. Provided a sufficiently large number of patients has been included in the trial, difference between sputum conversion rates of 70% and 72% in two drug schedules may well turn out to be statistically significant. Yet the difference is so slight that it may not be worth bothering about and the medical worker may well be justified in preferring the schedule with 70% conversion if it has other advantages.

Considering the stress laid on proper planning of studies, one might well get the impression that studies on unplanned data are, at best, a waste of time. This, however, is not always true. Retrospective studies necessarily have to deal with unplanned data and may be inescapable in many cases. The analysis of Data from such studies however is a very complex task. It is necessary to scrutinize the data in detail to eliminate possible source of bias. It is not unusual that a finding which appears plausible on the face of it may turn out to be unwarranted on closer examination. Spurious associations in particular have to be guarded against. An example may be worth quoting here. Some years back we at the New Delhi TB Centre were interested in finding out whether the pattern of tuberculous disease had changed materially over the years. To this end, x-rays of a sample of cases reporting in

the nineteen forties were to be compared with those of a similar sample from recent years by a panel of readers. Some x-rays in the former sample could not be traced, which fact tentatively was ascribed to faulty storage. Since no bias was suspected, it was decided to go ahead with the comparison of the available x-rays. This revealed a rather surprising finding: that contrary to the general impression there were not many cases with far advanced disease in the older series. Further scrutiny brought out the fact that in the 1940s, it was not considered worthwhile in the New Delhi TB Centre to take x-rays of cases with very far advanced disease. Because of the wartime scarcity of x-ray films, and the comparatively poor prognosis of such patients, they were usually diagnosed by fluoroscopy and sputum examination, no permanent x-ray record being considered necessary. Obviously, further analysis of this data had to get round this difficulty. Pitfalls like this are not at all rare in analysis of unplanned data and the investigator has to make assurances doubly sure before drawing any conclusions. For this and other reasons, retrospective studies should not be undertaken as an easy way out when properly designed prospective studies are possible and feasible.

After the completion of analysis, findings have to be presented either in the form of a paper in a journal or as a personal communication to a scientific conference. The technique of writing research papers is not really difficult to acquire. Papers, above all, should be readable and simplicity should be aimed at, even if it needs a special effort. The question of the size and number of tables and charts is important, as we will presently discuss, but no less important is that of a lucid exposition in the text. Indeed, the finest papers are those where tables etc. do not impede the line of reasoning and can even be dispensed with for a preliminary reading.

It is difficult to lay down any rules regarding the number of tables and diagrams but too liberal a use of these certainly gives rise to a sort of 'consumer resistance'. There is also the danger that with too many tables and charts-one may be unable to see the wood for the trees. In general, tables in the text should be brief and purposeful; the subsidiary ones are better relegated to the Appendix. Each table should be complete in itself, i.e., relevant information such as abbreviations and units used, period covered, whether a certain rate is per cent or per thousand, or per thousand per year, etc. should be given, within the table if possible, in footnotes if necessary. Graphs,

bar diagrams etc. are sometimes very useful for driving home a point but their use as a routine or as a substitute for tabular data is to be avoided. Serious minded readers sometimes want to make some additional calculations on their own and only tabulated data rather than sterile diagrams can serve this purpose.

Having made a plea for brevity, it now remains, paradoxically, to enter a caveat about the dangers of going to the other extreme. Instances are not rare of papers—and I mean papers with a statistical aspect—published with the sketchiest of data. Quite often, the idea at the back of the mind is that figures are boring things and ‘let us get them over while the fit is on us’. This suggests a casual, almost frivolous, attitude to the whole business of research and only the uncritical can be taken in by such logic. The discerning reader is apt to ascribe lack of relevant data to ignorance of the research discipline, or worse.

What has been said so far refers specially to papers meant for publication. Further problems arise when a paper has to be presented in a conference instead of being printed in a journal. As the time is limited, material for

presentation has to be judiciously pruned. Only the most important tables and diagrams can be presented. These, again, should be as simple as possible, each single slide containing only the minimum quantity of figures needed to make a point. It must be remembered that the human eye can take in only a limited quantity of statistical data at a time— specially when each slide is projected for just about 30 seconds. If too much mental effort is required to study a table or follow an argument many in the audience would rather give up. Since it is the speaker who is primarily interested in ‘selling’ his paper, it is for him to forestall audience apathy.

I am quite conscious that it is no easy task for most clinicians to work up any enthusiasm for figures and statistical methods. It will not be a bad beginning if these are accepted even as a necessary evil. For, in the words of Bradford Hill, “In both clinical and preventive medicine, and in much laboratory work, we cannot escape from the conclusion that they (figures) are frequently cogent, that many of the problems we wish to solve *are* statistical and that there is no way of dealing with them except by the statistical method”.

## AGAR ELECTROPHORESIS OF SERUM PROTEINS IN PULMONARY TUBERCULOSIS

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### Introduction

Reversal of serum albumin-globulin ratio in a wide variety of diseases caught the fascination of research workers and gave them an impetus to penetrate into the intricate mechanisms, if any, involved. Much breakthrough was made since a number of earlier workers reported such a reversal in pulmonary tuberculosis employing the conventional techniques of salt fractionation then in vogue (Eichelberger & McCluskey, 1927 ; Gutman et al 1936 ; & Bing, 1940) The development of electrophoretic technique of serum protein fractionation by Tiselius in 1937 brought in a revolutionary change in the concept of albumin-globulin ratio reversal and afforded the research workers a more meaningful tool to understand the complex field of protein biosynthesis and protein alternations in health and diseases. Luetscher (1941) was the first to report electrophoretic studies in pulmonary tuberculosis. He found decreased albumin, increased alpha and gamma globulin levels in his cases. By and large it appears that increase in alpha-2 globulin is the characteristic finding in pulmonary tuberculosis, although observations regarding alternations in the other protein fractions are conflicting. The present study was undertaken to study the changes in serum proteins in pulmonary tuberculosis employing agar electrophoretic technique and to correlate, if possible, the protein fractions with E.S.R. and C-reactive protein value.

### Materials and Methods

Thirty three patients attending the Wenlock Hospital, Mangalore, were selected for the present study. The pulmonary lesions were subdivided into minimal (referred to as early by us) and moderately advanced (referred to as advanced by us) in accordance with the classification of National Tuberculosis Association. All the patients came from the low middle class and lower classes of society. Their nutritional status was low. No attempt has been made to group the cases according to age, or sex because of the small number of subjects. A group of twenty normal blood donors has been included to serve as control.

On the morning of the day of the test,

5 ml. of blood was collected and allowed to clot at room temperature. In most cases the sera were subjected for analysis, when it was not possible to analyse on the same day the sera were kept frozen till they were analysed.

Total serum proteins were estimated by the biuret method of Kingsley (1942). Electrophoresis was done according to the method described by Giri (1956). The electrophoretogram so obtained was scanned by photoelectric densitometer. A graph was constructed with the densitometric readings as the abscissa and the distance in millimeter as the ordinate (Fig. 3 and 4). Alpha-1 globulin moved almost along with the albumin fraction, therefore it was included in the albumin value. The exact concentration of each protein fraction was then obtained from the total protein value.

E.S.R. for the first hour was estimated by Westergren's method. The presence of C-reactive proteins was qualitatively determined by slide-latex fixation test using latex anti C-reactive protein reagent manufactured by Hyland Laboratories, Los Angeles, California, U.S.A. The test was performed as per directions provided with C-reactive protein kit.

### Results

Electrophoretic serum protein values, E.S.R. and C-reactive protein values of the 33 tuberculosis patients and 20 normal controls are presented in Table I—III. The mean total protein value of 33 tuberculosis cases is  $5.597 \pm 0.446$  (S.E. Mean 0.079) and that of the normal controls is  $6.245 \pm 0.647$  (S.E. mean 0.148). Statistical analysis of the values revealed that the decrease in the total protein values in tuberculosis is highly significant with a 't' value of 4.225 (Table I). The observed decrease of the mean albumin value in the tuberculosis patients as compared to the normal controls is not statistically significant. Similarly the apparent increase in the average A/G ratio and the decrease of albumin/alpha-2 globulin ratio of the tuberculosis patients over the corresponding average values for the normal group is not statistically significant. However, the increase in alpha-2 globulin value and the decrease in beta and gamma globulin

TABLE I

Mean and standard deviation of protein and electrophoretic values of 33 Tuberculosis patients and 20 normal controls

		Tuberculosis cases	20 Normal controls	Difference in means of patients and controls
Total Protein	Mean	5.597	6.245	-0.648** (t=4.225)
	S.D.	0.446	0.647	
	S.E.	0.079	0.148	
Albumin	Mean	2.836	3.050	-0.214 N.S.
	S.D.	0.661	0.237	
	S.E.	0.117	0.055	
Alpha-2 Globulin	Mean	0.963	0.580	0.383** (t=3.524)
	S.D.	0.415	0.415	
	S.E.	0.082	0.033	
Beta-Globulin	Mean	0.517	0.830	-0.3134** (t=4.727)
	S.D.	0.318	0.168	
	S.E.	0.056	0.037	
Gamma-Globulin	Mean	1.280	1.735	-0.455** (t=3.411)
	S.D.	0.517	0.504	
	S.E.	0.076	0.116	
A/G Ratio	Mean	1.167	0.977	0.190 N.S.
	S.D.	0.626	0.165	
	S.E.	0.111	0.038	
Albumin/Alpha-2 ratio	Mean	4.313	5.500	-1.187 N.S.
	S.D.	3.626	0.987	
	S.E.	0.641	0.226	

Note : N.S. — Not significant  
 \*\* — Highly significant P 0.01  
 The t — Test for the difference of means is used in all these.

values of the tuberculosis patients compared to the normal group is highly significant with 't' values of 3.524, 4.727 and 3.411 respectively.

Statistical analysis of the E.S.R. and electrophoretic protein fraction of the 25 advanced and 8 early cases have been presented in table II with a view to find out whether it is possible to assess the severity of disease as classified. It can be seen from the table that except albumin/alpha-2 globulin ratio all other findings show statistically insignificant variation. In the case of albumin/alpha-2 globulin ratio early cases of tuberculosis have a mean value of 5.314±5.116 with a 't' value of 2.767. This increase is highly significant.

In table III are given the mean values of E.S.R. and electrophoretic protein fractions for the 24 C-reactive protein positive and 9 C-reactive protein negative cases of the tuber-

culosis group. No statistical significance has been observed using the 't' test.

Fig. 1 depicts the E.S.R. values of the T.B. patients with positive and negative C-reactive protein. Fig. 2 indicates the total protein values of the T.B. patients with positive and negative C-reactive protein values. As evidenced from the diagrams there is no cluster of points at any place ; both the positive and negative values are scattered and hence statistically insignificant. Similarly no significant correlation could be obtained when positive and negative C-reactive protein cases were correlated with other electrophoretic protein fractions. Figs. 3 and 4 show the typical electrophoretograms obtained for a normal and tuberculosis serum. The results have been summarised in table IV.

TABLE II

Mean and standard deviation of E.S.R., total protein and electrophoretic values of Tuberculosis patients

	Mean $\pm$ standard deviation of			Difference in mean of advanced and early cases	
	25 advanced cases	8 early cases	all 33 cases		
E.S.R. (m.m. for 1st hour)	88.44 $\pm 23.976$	78.62 $\pm 28.115$	86.06 $\pm 25.349$	9.82	N.S.
Total Protein (gm%)	5.652 $\pm 0.433$	5.425 $\pm 0.444$	5.597 $\pm 0.446$	0.227	N.S.
Albumin	2.804 $\pm 0.653$	2.938 $\pm 0.675$	2.836 $\pm 0.661$	-0.134	N.S.
Alpha-2 Globulin	0.965 $\pm 0.441$	0.955 $\pm 0.532$	0.963 $\pm 0.415$	0.010	N.S.
Beta Globulin	0.567 $\pm 0.334$	0.360 $\pm 0.182$	0.517 $\pm 0.318$	0.207	N.S.
Gamma Globulin	1.3140 $\pm 0.469$	1.173 $\pm 0.292$	1.280 $\pm 0.517$	0.141	N.S.
A/G ratio	0.105 $\pm 0.591$	1.361 $\pm 0.689$	1.167 $\pm 0.626$	-0.256	N.S.
Albumin/A lpha-2 ratio	3.993 $\pm 2.923$	5.314 $\pm 5.116$	4.313 $\pm 3.626$	-1.321	** (t = 2.767)

Note : N.S. — Not significant  
\*\* — Highly significant: P 0.01

## Discussion

Intensive study of the distribution of serum proteins in tuberculosis has received the attention of many workers. Evidence has been established that in "active infection", significant changes in serum proteins occur. Gaitonde et al (1959) and Bovornkitti (1962) have reported a fall in total protein level in pulmonary tuberculosis. We have observed a similar fall in our cases of pulmonary tuberculosis. The decrease in our series of 33 cases when compared with normal group is highly significant with a 't' value of 4.225 (Table I). This indicates poor nutritional status of tuberculosis patients. The fall in total protein levels has been reported to be progressive from minimal to advanced cases (Bovornkitti 1962). However, this fall in our series is not progressive since the value in early cases is 5.425 gs% whereas, in advanced cases it is 5.652 gs%.

It is believed that in most of the infectious diseases there is a reversal of the albumin-globulin ratio. Our results in pulmonary tuberculosis do not subscribe to such a belief. Agar electrophoretic study of the serum protein changes in our series has shown that there is no statistically significant decrease of albumin value in tuberculosis patients compared to normal or between advanced and early cases.

The most striking finding of our results is the abnormality found in the globulin fractions. Raised levels of alpha-2 globulin has been the most consistent finding. This observation is in confirmity with those of others (Gaitonde 1959, Bovornkitti 1962, Seibert 1942, Volk 1953, & Gilliland 1956). The increase in alpha-2 globulin fraction represents tissue destruction (Seibert 1947) and therefore it can be said that pulmonary tuberculosis sets in tissue destruction in the host. This is so even in early

AGAR ELECTROPHORESIS OF SERUM PROTEINS IN PULMONARY TUBERCULOSIS

TABLE III

Mean and standard deviation of the protein and electrophoretic values of T.B. cases with positive and negative C-reactive protein

Characteristic Studied	C-Reactive Protein Positive (24 values)		C-Reactive Protein Negative (9 values)	
	Mean	Standard deviation	Mean	Standard deviation
E.S.R. (mm for 1st hour)	86.38	27.14	85.22	23.21
Total Protein	5.538	0.438	5.756	0.429
Albumin	2.729	0.576	3.122	0.777
Alpha-2 Globulin	0.981	0.467	0.916	0.454
Beta-Globulin	0.563	0.316	0.393	0.285
Gamma Globulin	1.267	0.471	1.314	0.309
A/G. ratio	1.068	0.540	1.432	0.750
Albumin/Alpha-2 ratio	3.948	3.041	5.287	4.745

For each of the characteristic studied above the difference between the mean of positives and of negatives is found to be NOT SIGNIFICANT by using t — tests

There is no correlation between the C-reactive protein and any of the above characteristics.

TABLE IV

Table showing summary of the results

	Total Proteins	Albumin	GLOBULINS			A/G. ratio	Alb./alpha-2 ratio
			Alpha-2	Beta	Gamma		
Pulmonary T.B. total number of cases compared with normal	↓	↓	↑	↓	↓	↑	↓
Pulmonary T.B. early cases compared with advanced cases	↓	↑	↓	↓	↓	↑	↑
Pulmonary T.B. advanced cases compared with early cases	↑	↓	↑	↑	↑	↓	↓

Continuous and broken arrows show significant and insignificant direction of alteration respectively.

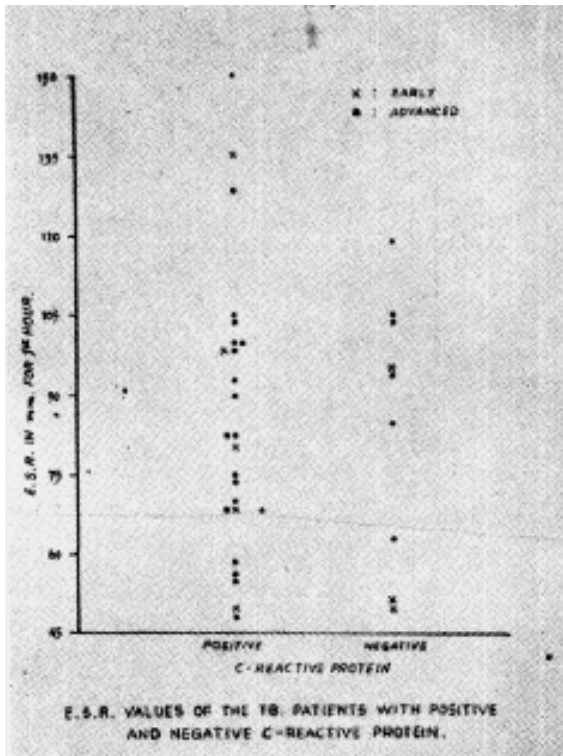


Fig. I

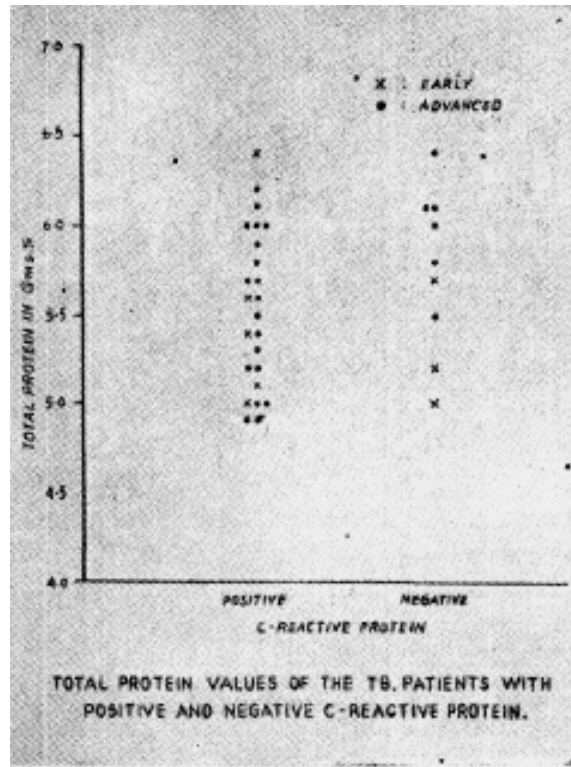


Fig. II

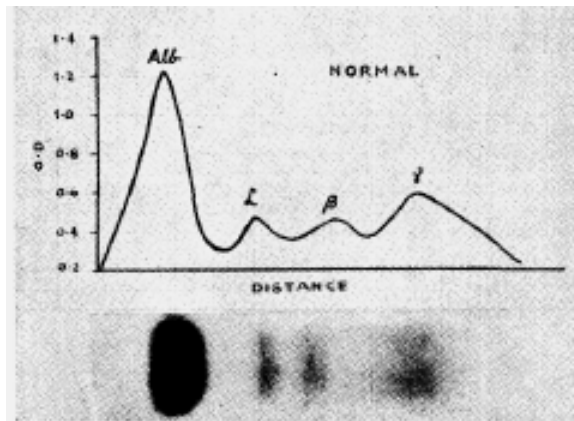


Fig. III

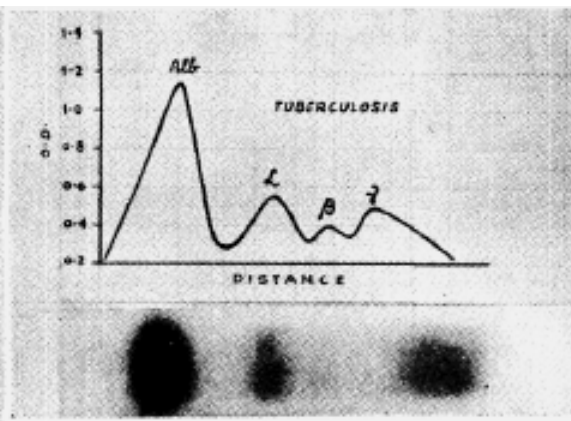


Fig. IV

stages of the disease. The stage of the disease process, however, cannot be definitely assessed since there is no correlation in our series between the values and the severity of the lesions.

Beta globulin values tend to fall in tuberculosis group as compared to the normal group. The decrease is significant with a 't' value of 4.727. The decrease is more marked

in the early stage of the lesion (table I). This observation is not in conformity with the findings of other workers who observed a significant elevation of beta globulin fraction in severely ill patients (Gaitonde 1959, Volk 1953, Seibert 1947). However, Baldwin and Hand (1953) have also observed a decrease in the beta globulin component. Since the increase of beta globulin is generally associated with liver damage, the differing observations may

not be ascribed primarily to pulmonary tuberculosis. Further work is necessary to implicate elevated beta globulin as a secondary effect of pulmonary tuberculosis or otherwise.

There is significant fall of gamma globulin fraction with a 't' value of 3.411. This finding is not in agreement with other workers who have all reported an increase of this fraction in all cases of active pulmonary tuberculosis. Seibert et al (1942) have ascribed the rise to be an indication of resistance to the disease. It is generally known that increased gamma globulin is a common characteristic of most hepatic disease (Agarwal 1957, & Popper 1951) and that liver impairment is present in advanced tuberculosis (Hurst 1947, & Small 1950). Accordingly the elevation found by other workers could partly be explained by liver alteration. Since our series did not include far advanced cases, it is likely that they did not have associated liver alteration. Since our series did not include far advanced cases, it is likely that they did not have associated liver alteration. However, the significantly low value obtained by us remains to be explained.

The clinical status is better correlated with albumin/alpha-2 globulin ratio and it is considered to be a better criterion of the severity of the disease process. We have also observed albumin/alpha-2 globulin ratio fall in tuberculosis when considered as a whole. But this alteration is not statistically significant. However, there is a definite and significant fall of this ratio in the advanced stage of the disease (Table I). Thus our observation is in conformity that the albumin/alpha-2 globulin ratio is a better criterion of the severity of the disease process as observed by other workers.

That E.S.R. value cannot be correlated with the protein fractions and the severity of the disease is evident from Table II. Our findings are in agreement with Gaitonde (1959), & Gilliland (1956) that correlation of the clinical status with albumin/alpha-2 globulin ratio is a better index than with E.S.R.

Although biochemical study of the alteration of the serum protein fractions in pulmonary tuberculosis alone do not prove to be of diagnostic value, they will fruitfully assist in establishing the therapeutic efficacy and the severity of the lesion. "The protein spectrum in plasma and serum is the resultant of a host of factors concerned with the formation, the interaction, and the destruction of the individual components". It remains, however, to be established what interplay of mechanisms are responsible for the alterations in the different globulin fractions.

### Summary

Fractionation of serum proteins by agar electrophoresis has been done in 20 normal controls and 33 patients of pulmonary tuberculosis prior to treatment with anti-tuberculosis drugs. The results clearly demonstrate that there are definite changes in serum proteins from normal values in tuberculosis. A significant fall in total proteins, beta and gamma globulins and a rise in alpha-2 globulin has been consistently observed. Albumin/alpha-2 globulin ratio in advanced cases has been found to be significantly lower than that of early cases.

### ACKNOWLEDGEMENT

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## ETHIONAMIDE AND ISONIAZID IN THE MIDDLE-AGED AND THE ELDERLY PATIENTS

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### Introduction

A combination of streptomycin and isoniazid is very effective in the initial treatment of pulmonary tuberculosis. However, streptomycin, since it is given by injection, has obvious drawbacks in ambulatory therapy. There are villages where the patients have to walk miles to get their daily injection. The charge for injection adds to the cost of treatment. Again, streptomycin is not a very suitable drug for the middle aged and the elderly patients due to high incidence of vestibular and cochlear toxicity.

Encouraged by the report of British Tuberculosis Association/Hong Kong Tuberculosis Treatment Services (1964) on ethionamide and isoniazid in newly diagnosed previously untreated cases of pulmonary tuberculosis, it was decided to assess the role of this combination in the middle-aged and the elderly cases of pulmonary tuberculosis.

### Material And Methods

The material for the present study consisted of 50 cases of pulmonary tuberculosis whose ages ranged from 50 to 85 years (average 62 years). 44 were men and 6 women. 2 cases were, however, withdrawn from the trial as they were found to have had previous treatment with anti-tubercular drugs. Another 3 cases were withdrawn early in the trial as they did not stick to the protocol ; a totally oral regime did not appeal to them and they were getting streptomycin injection from other sources.

All the cases were placed on 400 mg. isoniazid and 500 mg. of ethionamide daily given as a single dose at bed time. Isoniazid was given as four 100 mg. tablets and ethionamide as four 125 mg. sugar coated tablets. Although higher strength ethionamide tablets are also available, 4 tablets of each drug was thought to lessen the chances of misunderstanding about instructions. It was proposed to continue the combination for one year. The drugs were supplied free of cost to the patients.

The patients were closely questioned about the history of previous treatment, if any. Only those who had not received any specific therapy

were included in the study. Moribund patients were excluded from the trial.

Sputum was examined for AFB using the Ziel-Neelson technique. Only smear positive cases were included. As the culture facilities in the department are inadequate and unreliable, no culture examination was done. Smear examination was repeated once a month and, if found negative, further specimens were examined on three consecutive days. If no AFB were demonstrable in all the specimens, the case was adjudged as bacteriologically negative. If bacteriological conversion was not obtained at four months and especially if there was also evidence of clinical or radiological deterioration, the case was withdrawn from the study, having been adjudged as treatment failure.

A chest radiograph was taken in the beginning in every case to assess the extent and type of the disease. Only moderately advanced or far advanced cases were selected for the trial ; minimal cases were excluded as excellent results have been reported with isoniazid alone in such cases. The skiagram was repeated every three months and at the time of sputum conversion.

All the patients were unhospitalized throughout the course of their treatment. They collected drugs for one week in the first instance and if no side effects to the drugs were complained of, they were supplied drugs for a fortnight at a time.

On each visit the progress was assessed clinically ; radiographs and sputum examinations were ordered as outlined above. Any symptoms or signs suggestive of drug toxicity were noted ; to avoid suggestion no attempt was made to elicit symptoms by direct questioning.

### Observations And Results

As mentioned above 5 cases were excluded early in the trial due to various reasons. Thus only 45 cases were assessed. Of these 23 had moderately advanced disease and 22 had far advanced lesion. 12 cases also suffered from chronic dyspepsia, 3 had diabetes mellitus (1 with neuropathy and nephropathy also) and 4 had history suggestive of chronic bronchitis.

### A. Efficacy of Treatment (Table Nos. 1 & 2)

Of the 45 cases, 2 cases had to be withdrawn due to intolerance to the drugs (presumably to ethionamide), so that efficacy of treatment was assessed in 43 cases only.

Clinical improvement, as shown by relief in chest symptoms and toxemic manifestations were noted in 42 out of 43 cases. 3 of these deteriorated later.

All the cases had cavitory disease on admission to the trial. In 97.6% there was radiographic improvement, assessed by clearing of shadows and/or diminution in size of the cavities. In 31 cases (72%) cavities disappeared completely while in others they were markedly reduced in size. The maximum improvement was noted in the first three months although further radiological clearing continued to occur upto nine months.

Sputum converted in 39 cases (90%). In 25 this occurred in first 2 months, in 10 in the third month and in 4 in the fourth month. The speed and incidence of sputum conversion was the same in moderately advanced and in far advanced cases. All the 39 cases maintained the bacteriological improvement, 35 cases completed treatment for full one year, 3 cases for 9 months and one for 8 months. The four cases who responded to treatment but did not complete full one year treatment did not report for collection of drugs and could not be traced.

### Drug Toxicity and side effects (Table No. 3)

Adverse reactions to the drugs were common but were not serious enough to need withdrawal of the drugs except in two cases.

A metallic taste in the mouth, anorexia, nausea or vomiting was complained of by 9 cases (19.9%). In 2 cases the symptoms were persistent and intractable and the patients refused to continue the treatment. In the other 7 the symptoms became less or disappeared in course of time.

Burning sensation in the palms and soles and pain in the limb were complained by 2 cases (4.4%). These symptoms were controlled with 10 mg. pyridoxine hydrochloride per day while the anti-tubercular drugs were continued. In no case there was objective evidence of neuropathy.

In 2 cases (4.4%) a transient rash and itching occurred which was attributed to

TABLE 1

*Showing the results of treatment*

Total number of cases—43

	No. of cases	Percentage
Clinical improvement	42	97.6
Radiological improvement	42	97.6
Bacteriological conversion	39	90.0

TABLE 2

*Showing the bacteriological response in relation to extent of disease*

Total number of cases—43

Extent of disease	No of cases	No. of cases converted	Percentage
Moderately advanced	21	19	90.0
Far advanced	22	20	90.0

TABLE 3

*Showing the adverse reactions to drugs*

Total number of cases-43

Nature	No. of cases	Percentage
Gastrointestinal		
Persistent	2	4.4
Minor	7	15.5
Neuropathy (Subjective)	2	4.4
Allergic	2	4.4
Miscellaneous	6	13.3

allergy to one of the drugs. However, these symptoms could be controlled by small doses of anti-histaminics.

3 cases complained of drowsiness and lethargy ; one of them was a diabetic. Another 2 cases complained of heaviness in the head. Gynecomastia with acne was noted in one case. These symptoms needed re-assurance only.

No case of jaundice or exfoliative dermatitis was noted in the present series.

## Discussion

In the present study 400 mg. isoniazid and 500 mg. ethionamide was given orally in a single dose at bed time in middle aged and elderly patients of pulmonary tuberculosis who were not previously treated with anti-tubercular drugs. The dose of ethionamide is smaller than used in the British Tuberculosis Association (1961) investigation. There is a good experimental support for using small doses of ethionamide with isoniazid. Thus Mm. Grumbach (1963) concluding on the basis of experimental tuberculosis in mice recommends 400 to 500 mg. isoniazid (corresponding to 4 times the minimal effective dose) with 200 to 500 ethionamide. Again RIST (1964) as a result of laboratory experiments observed that in isoniazid-ethionamide combination isoniazid is the principal drug and should be given in high doses while 500 mg. ethionamide is adequate.

Initially 50 cases were selected for the trial. However, 5 cases did not satisfy the protocol and were withdrawn. Another 2 cases were withdrawn in the first fortnight due to gastrointestinal intolerance to the drugs. Thus efficacy of the drugs has been analysed in 43 cases and side effects to the drugs in 45 cases.

Sputum conversion was obtained in 39 of the 43 cases (Conversion rate 90%) who remained in the trial sufficiently long. If all the 45 cases are included, the conversion rate was 81.57%.

There are three other reports in the literature on the use of ethionamide-isoniazid combination in previously untreated cases. Our material, in [contrast to these reports, consisted of middle aged and elderly patients only. Again, while in the present report the doses of ethionamide and isoniazid were 500 mg. and 400 mg. respectively given in a single dose, Lees (1964) from Glasgow used 1 gm ethionamide with 400 mg. isoniazid, British Tuberculosis Association/Hong Kong Tuberculosis Treatment Services (1964) and Bhatia and Lal (1966) from Amritsar used 500 mg. ethionamide and 300 mg. isoniazid. While in the Hong Kong trial the drugs were given in a single dose, the Amritsar workers gave the drugs in two divided doses.

In the Hong Kong trial, sputum conversion was obtained in 98% of cases who continued the drug for one year, overall conversion rate was 85% including those who left off. Lees (1964) obtained sputum conversion in all the 32 cases. Bhatia and Lal (1966) noted a

sputum conversion in 77% of 13 cases at 6 months.

Gastrointestinal side effects were noted in 20% cases in the present report but except in two cases they were not troublesome enough to need withdrawal of the drugs. Thus in 500 mg. dose daily ethionamide was very well tolerated. Good tolerance was also observed in other series mentioned above. This is in marked contrast to the high incidence of intolerance in the British Tuberculosis Association trial (1961) of a combination of ethionamide, pyrazinamide and cycloserine. In a more recent study by the British Tuberculosis Association (1968J, again a high incidence of gastrointestinal symptoms were reported. In this study ethionamide was combined with streptomycin and isoniazid. The dose of ethionamide in both the trials was high. That the dose of ethionamide is one of the important factors in relation to the incidence of gastrointestinal side effects is also suggested by a trial of ethionamide, isoniazid and thiacetazone in drug resistant cases by the present author (Narang and Sarin, 1966). In this investigation 750 ethionamide in two divided doses was used and a high incidence of gastric upsets was observed. Other possibly important factors are the drug combinations and racial differences.

Allergic manifestations were uncommon and could have been due to ethionamide or isoniazid. Carey (1965) reports successful desensitisation in a case of ethionamide allergy.

Minor side effects included drowsiness, lethargy, heaviness in the head, gynecomastia and acne. Drowsiness may be a manifestation of hypoglycemia (British Tuberculosis Association, 1968). Hypoglycemia has been described in diabetic patients treated with ethionamide (Clark and O'Hea, 1961, Somner and Brace, 1962). Of the three patients in the present series, who complained of drowsiness, one was a diabetic. But investigations to exclude hypoglycemia were not done.

Clinical jaundice was not noted in a single case. This is especially striking considering that the 3 of the cases in the present study were known diabetics; the diabetics and the alcoholics are especially prone to develop hepatotoxicity (De Voogd, 1963). The low incidence of icterus has also been reported by other workers. However, routine liver function tests are likely to reveal abnormality in a higher percentage (Bhatia and Lal, 1966; Somner and Brace, 1967; British Tuberculosis Association, 1968). No routine liver function tests were done in the present study.

Some of the treatment failure cases might have been primarily resistant to one of the drugs. As sensitivity tests were not done, their incidence is not known. There is a very interesting relationship between isoniazid resistance and ethionamide. While low degree isoniazid resistant bacilli are sensitive to ethionamide, in man there is usually a high degree isoniazid resistance even in rapid inactivators so that ethionamide is likely to be effective in such cases. Canneti (1965) and Nazaki (1964) in experiments using H37Rv strain of mycobacterium tuberculosis resistant to 50 meg per cc. of isoniazid found that the combination of ethionamide and isoniazid had higher antibacterial activity against the test strain than ethionamide alone and observed decreased resistance of resistant strain to isoniazid. They confirmed these findings in male mice.

### Summary

The role of 500 mg ethionamide and 400 mg isoniazid, given in a single dose orally at bed time was assessed in 45 previously untreated middle aged and elderly cases of pulmonary tuberculosis. 90% sputum conversion was obtained. If those who fell out of the trial due to drug intolerance the conversion rate was 81.5%. The drugs, in the dosage given, were very well tolerated.

### ACKNOWLEDGEMENT

The author acknowledges the generous supply of ethionamide by M/s. Themis Pharmaceuticals.

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# A COMPARATIVE CLINICAL EVALUATION OF THE ROLE OF THIOACETAZONE AND PAS IN THE MANAGEMENT OF PULMONARY TUBERCULOSIS

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## Introduction

Thioacetazone has, during the last few years, raised many points of controversy. While its efficacy as tuberculostatic agent has been compared with that of PAS, its toxicity in vivo studies has been found to be variable (Miller Fox and Tall, 1966, Aquinas 1968 and Miller, 1968). It has been suggested that latter manifestations may vary with the dietary habits (Miller, Fox and Tall, 1966) and race. (Miller, Fox and Tall, 1966 and Aquinas, 1968).

We have been using Thioacetazone in various combinations in our hospital for the past 5 years, and have conducted a controlled trial on the relative efficacy of thioacetazone and PAS in the management of cases suffering from pulmonary tuberculosis. The present report pertains to that aspect of the problem.

## Material & Methods

390 cases suffering from pulmonary tuberculosis, admitted to Kasturba Hospital, were studied. These cases were divided by random sampling into two groups—one group was recipient of PAS in conjunction with other anti-tuberculosis drugs while the other received thioacetazone in place of PAS. Exact dosage and drugs schedules are given below:

All the cases at the initiation of trial had to fulfil following criteria:

2.1. Sputum must be positive for AFB (smear examination.)

2.2. Radiological picture should be compatible with the diagnosis of pulmonary tuberculosis with atleast one cavity in either infraclavicular region.

2.3. Every case was asked in detail regarding the amount of drug treatment he had received in past. Those who had taken less than 10 days of chemotherapeutic treatment prior to their admission to the hospital were labelled as 'untreated' and those who had more than 10 days' therapy were labelled as 'treated'.

2.4.1. The final distribution of cases was as follows (vide table No. 1).

2.4.2. According to previous treatment the distribution of cases was as follows (vide table No. 2).

2.4.3. According to various treatment schedules, the distribution of cases was as follows (vide table No. 3).

TABLE 1  
*Final distribution of cases*

	PAS Group	Thioacetazone Group
Total number of cases (Initial)	207	193
Cases dropped from trial	4	6
Reasons: Incomplete data	1	2
Incorrect History	1	1
Left against advice	2	3
Cases available for final analysis	203	187

TABLE 2  
*Distribution of cases according to previous chemotherapy received by the cases.*

	PAS Group	Thioacetazone Group
Untreated	108	91
Treated	95	96
Total	203	187

TABLE 3  
*Distribution of cases according to various schedules of treatment.*

	PAS Group		Thioacetazone Group	
	SPH	PH	STH	TH
Untreated	52	56	42	49
Treated	61	34	57	39
Total	113	90	99	88

*Schedule of Treatment*

S+T+H—Streptomycin 1G IMI once a day—Thioacetazone 150 mgms/day—INH 10 mgms/kg. body weight—vitamins (hitherto referred to as STH group).

T+H—Thioacetazone and isoniazid administered in the same dose as above (hitherto referred to as TH group).

S+P+H—Streptomycin and Isoniazid administered in usual dosage—PAS 10 G/day (hitherto referred to as SPH group).

P+H—PAS and INH administered in same dose as in SPH group (hitherto referred to as PH group).

After 3 months of daily injections of Streptomycin the injections were withdrawn and patients received only TH or PH group of drugs.

*2.5. Duration of Treatment*

Duration of therapy was 6 months in each case. All the cases had to stay in the hospital during the period of trial. 5 cases who had left the hospital prematurely had to be withdrawn from the present trial (vide Table No. 1).

*2.6. Investigations*

Sputum examination for AFB (Smear examination by ZN technique) was done every month. Gaffkey count was taken as a guide to progress.

Chest X-ray was repeated every three months.

2.7. Assessment of results were based empirically as under:

(a) *Improved*: Sputum conversion.

Sub-Group: Marked Improvement—Sputum conversion with disappearance of cavity.

Moderate: Sputum conversion with reduction in size of cavity.

Mild: Sputum conversion with cavity represented by a bullous cyst.

(b) *Stationery*: No sputum conversion, chest X-ray—same.

(c) *Deteriorated*: Deterioration on radiological and clinical grounds or development of toxic reactions to the chemotherapy.

**Results**

Final overall results have been depicted in Tables No. 4, 5 and 6.

**Discussion**

This study relates to hospitalised cases and extends over a period of six months' observation.

In the hospital itself drug administration was done by the trained nurses who would ensure regular intake of adequate dosage of drugs in their presence. While Thioacetazone

TABLE 4  
*Overall results at the end of six months' study.*

Results	Groups:			
	SPH (113)	STH (99)	PH (90)	TH (88)
Improved	72(64%)	60(61%)	56(62%)	46(52%)
Marked:	25(22%)	12(12%)	11(12%)	10(11%)
Moderate:	42(37.5%)	38(39%)	26(29%)	13(15%)
Mild	5(4.5%)	10(10%)	19(21%)	23(26%)
Stationary	22(18%)	15(15%)	11(12%)	9(10%)
Deteriorated	16(14%)	19(19%)	21(23%)	28(32%)
Expired	2( 3%)	2( 2%)	2( 3%)	1(1.5%)
Therapy changed	U 1%)	3( 3%)	—	4(4.5%)

TABLE 5  
Results of therapy in relation to previous chemotherapy received by the patient

Results	Groups							
	SPH		STH		PH		TH	
	Untreated (52)	Treated (61)	Untreated (42)	Treated (57)	Untreated (56)	Treated (34)	Untreated (49)	Treated (39)
Improved	50 (96%)	22 (36%)	36 (86%)	24 (42%)	47 (84%)	9 (27%)	34 (70%)	12 (31%)
(Marked)	21 (42%)	4 (6.5%)	10 (24%)	2 (4%)	11 (19%)	—	9 (18.5%)	1 (2.5%)
(Moderate)	28 (52%)	14 (23%)	23 (54%)	15 (25%)	26 (47%)	—	18 (37%)	—
(Mild)	1 (2%)	4 (6.5%)	3 (8%)	7 (13%)	10 (18%)	9 (27%)	7 (14.5%)	11 (28.5%)
Stationery	2 (4%)	20 (33%)	4 (9%)	11 (19%)	6 (10%)	5 (14%)	2 (4%)	7 (18%)
Deteriorated	—	16 (26%)	2 (5%)	17 (30%)	2 (4%)	19 (56%)	12 (24%)	16 (41%)
Expired	—	2 (3%)	—	2 (4%)	1 (2%)	1 (3%)	—	1 (2.5%)
Changed therapy	—	1 (2%)	—	3 (5%)	—	—	1 (2%)	3 (7.5%)

ROLE OF THIOACETAZONE AND PAS IN PULMONARY TUBERCULOSIS

TABLE 6  
*Toxic manifestation*

	SPH (113)	STH (99)	PH (90)	TH (88)
1. Ototoxicity (Vestibular Damage)	3	8	—	2
2. Cutaneous Rashes	—	5	—	3
3. Cutaneous rashes severe enough to warrant a withdrawal of drugs.	—	2	—	1
4. Hepatic toxicity (Jaundice)	—	3	1	3
5. G.I. Intolerance (Mild)	2	5	3	8
6. Peripheral Neuritis	1	2	1	1

*N.B.*

1. One case in STH group died due to severe hepatic damage passing on to hepatic coma.
2. One case in STH group and one in TH group developed such a severe cutaneous reactions that withdrawal of therapy and administration of corticosteroids had to be resorted to, in an attempt to save their lives.

and isoniazid tablets were swallowed in a single dose, PAS and INH were given in 2 divided doses administered after meals. Thus, the problem of drug default was almost completely eliminated. However, since the bulk of PAS and Isoniazid was quite different from that of Thioacetazone and Isoniazid, it was not possible to perform a double blind trial on the subject.

A glance through table Nos. 4, 5 and 6 reveals certain outstanding features. These can be summarised as under:

4.1. Clinical response to Isoniazid and Thioacetazone combination was poorer as compared to that of Isoniazid and PAS group. This was especially true for those cases who had not received previous treatment with anti-tuberculosis drugs.

Culture and sensitivity studies on tubercle bacilli were not done although the facilities for the same did exist in our hospital. During the trial our attempts were to create condition which can be reproduced in any hospital. Most of the cases getting admitted to our hospital are those who have been grossly (and irregularly) treated in the past without deriving any benefit. They have meagre resources at their command and may not be able to afford second line of anti-tuberculosis drugs (e.g.

viomycin, cycloserine, pyrazinamide, ethionamide, kenamycin, ethambutal etc.). Further tolerance to these drugs is very poor. Therefore, irrespective of the drug resistance pattern of the tubercle bacilli excreted by the patient, an attempt was made to evaluate the efficacy of Thioacetazone in combination with Isoniazid alone or in conjunction with Streptomycin. The results in the irregularly treated group of the cases are disappointing and are certainly not better than PH or SPH groups.

4.2. The tolerance to thioacetazone was poorer as compared to that of PAS. Both major and minor toxic reactions were met with much more frequently in the former series.

4.2.1. Jaundice appeared during thioacetazone therapy in six cases (2 cases in untreated group and 4 in treated group) as compared to that of one (belonging to untreated group) case in PH group. In one case of the former group, the patient passed on to hepatic coma and could not be saved. However, in remaining five cases belonging to TH group thioacetazone in test dosage (1 mgm.) was again started after the remission of jaundice. There was no recurrence of jaundice. Thereafter, full dose of thioacetazone was instituted. This led us to conclude that jaundice in these cases could have been due to some other cause (e.g. infective hepatitis or homologous serum

jaundice). However, its predominance in the thioacetazone group might be regarded to indicate a casual relationship. It is also likely that hepatotoxicity due to thioacetazone might be due to cumulative toxic reactions of the drug and it might not have re-manifested itself during the remaining period of hospitalisation of the patients.

4.2.2. Severe exfoliative dermatitis was met with in 3 cases in the thioacetazone group (all belonging to 'treated' group). In two cases withdrawal of drug and symptomatic therapy failed to produce any improvement. 60 mgms Prednisolone per day had to be instituted to save their lives. These cases were later withdrawn from the group. Reinstitution of isoniazid and streptomycin was not followed by any cutaneous reaction in this group of cases. However, we avoided further use of thioacetazone in them.

4.2.3. Thioacetazone group of cases suffered from toxic reactions to streptomycin on 8th nerve more frequently as compared to that of PAS group.

Potential of ototoxic reaction of streptomycin by thioacetazone (not by isoniazid, because it was a common drug in both the groups) permits us to conclude that combination of thioacetazone and streptomycin should be avoided in presence of obvious renal damage and in persons beyond the age of 40 years. Of 8 cases in the STH group who had developed this toxicity 5 were beyond 40 years of age. Two cases receiving thioacetazone and isoniazid alone developed ototoxic reactions (vestibular damage). This implies that thioacetazone besides potentiating the vestibular damage due to streptomycin, could by itself damage the vestibular system independently: although the number of cases is too small to arrive at a definite conclusion (Deshmukh and Master, 1962, Miller, Fox and Tall, 1966 and Miller, 1968).

The study permits us to conclude that on clinical grounds thioacetazone is inferior to that of PAS and is more toxic than PAS (with reference to both minor and major toxic reactions).

This observation, however, may not apply universally in all the cases of pulmonary tuberculosis because it has been demonstrated that tolerance to thioacetazone may depend on race (Aquinas, 1969), nutritional status of the host and many other factors. The international

study on thioacetazone (Miller et al, 1966) has already emphasised these points and has further emphasised that before embarking on a mass scale use of this drug on a domiciliary basis, its tolerance in that particular community must be ascertained. Our study has demonstrated that thioacetazone is not so well tolerated as PAS at least by the residents of Uttar Pradesh, and that it is liable to lead to serious toxic reactions which may occasionally be fatal.

#### Summary

390 cases suffering from pulmonary tuberculosis admitted to Kasturba Tuberculosis Hospital were divided into four groups by random sampling. 203 cases received PAS (10 gm/day) and isoniazid (400 mgms/day), 113 received streptomycin (1 G IM17 once a day) for first 3 months of observation in addition. 187 cases received Thioacetazone (150 mgms/day) instead of PAS along with isoniazid (in usual dosage), 99 received streptomycin also. Our study extended over a period of six months and all along these cases were hospitalised. It was noted that the response to thioacetazone was inferior to that of PAS particularly in those cases who had not received chemotherapy in past. Further, the tolerance to thioacetazone was found to be poorer than that of PAS.

#### ACKNOWLEDGEMENTS

The author is grateful to Drs. J. Nath and S.P. Misra for their cooperation in the trial. His grateful thanks are also due to M/s. Unichem Laboratories for the liberal donations of Unithiben VF tablets containing Thioacetazone, isoniazid, antihistamine and vitamins.

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## NEWS & NOTE

### Annual Meetings

The Thirteenth Annual General Meeting of the Tuberculosis Association of India was held on 18th April at 11.30 A.M. in the Conference Hall of the Association. Dr. S. Chandra-sekhar, the President of the Association, presided. The Chairman of the Association presented the report on the working of the Association during 1968 and the Honorary Treasurer presented the accounts. The meeting elected members to the Central Committee as provided for in the rules.

The Conference of the Secretaries of the State TB Associations and Seal Sale Organisations in India was held in the Conference Hall of Association at 3.00 P.M. on 18th April and the Technical Committee of the Association met on 19th April.

### VII Maharashtra Conference

The Maharashtra State Anti-TB Association organised a two-day State TB and Chest Diseases Workers Conference in Bombay from 22nd to 24th March, 1969. The Conference which was inaugurated by Dr. P.V. Cherian, the Governor of Maharashtra was addressed by Smt. Pratibha D. Patil, Deputy Minister for Public Health and Prohibition. Dr. P.K. Duraiswamy, Director General of Health Services and Chairman of the Tuberculosis Association of India, also addressed the conference.

Shri B.M. Cariappa, Secretary-General, Tuberculosis Associations of India, was the President of the Conference. Shri Cariappa's address covered the role of voluntary TB Associations in India with special reference to Maharashtra.

Discussions included 'Control of Tuberculosis in rural areas' in which Dr. B.B. Yodh and P.A. Deshmukh participated. Dr. M.D. Deshmukh and Dr. J.C. Kothari took part in the discussion on 'Place of Thiacetazone in treatment of Pulmonary Tuberculosis'. In another discussion on 'Tuberculosis in Children' Dr. M.M. Wagle and Dr. M. Asher participated.

The Conference concluded with a Meeting of the Secretaries of District Associations in Maharashtra.

On the occasion of the conference the Maharashtra Association brought out an interesting handbook on Tuberculosis.

Shri B.M. Cariappa, the Secretary-General, also visited Goa and attended a meeting of the Executive Committee of Goa Association and addressed the Rotarians and Care-Committees in Panjim.

### West Bengal Conference

The Bengal Tuberculosis Association held the 2nd West Bengal TB Conference from 12th to 14th April, 1969 in Calcutta. The conference included three symposia, and a few original papers were also presented.

On this occasion, the Association brought out an attractive Souvenir containing useful information on the development of tuberculosis services in the State. The Association also inaugurated at this time a special chest clinic for children, the first of its kind in India containing advanced laboratory facilities for 42 affiliated chest clinics. The three-storeyed building was built at a cost of Rs. 2,25,000.

### Conference in Assam

The TB Association of Assam will be holding a Seminar on Tuberculosis shortly. The Seminar is likely to be attended by Dr. P.K. Duraiswamy, Director General of Health Services, and Shri B.M. Cariappa, Secretary-General, Tuberculosis Association of India.

### Award to Dr. R. Viswanathan

Dr. R. Viswanathan, Emeritus Scientist, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, has been awarded the Eugenic Morathe Prize by Academia De Lincie of Italy, for outstanding contribution in the field of Tuberculosis and Chest Diseases. The prize has been awarded only to three other distinguished scientists so far in the world. Dr. Viswanathan is the first non-Italian to receive the Award, the value of which is two million Liras.

### Seal Sale Award—1969

The 1969 Trophy for the highest Seal Sale collections, was awarded to the Tamilnadu TB Association. The Trophy was presented to the Association at the time of the Annual General Meeting of the Association held on 18th April, 1969.

### Proceedings of the XXIII TB Conference

Copies of the Proceedings of the Twenty-third Conference held in Bombay in 1968 are

available for sale from the Tuberculosis Association of India, 3-Red Cross Road, New Delhi-1. The price per copy is Rs. 23/- plus postage.

#### **Chest Diseases' Prize Award**

The Indian Association for Chest Diseases has instituted a cash prize of Rs. 200 to be given to the author of the best article published during the previous year either in Indian or foreign Journal on any subject in the speciality of chest diseases. The prize is open to only those who are under the age of 40 years. The work on which the article is based must have been conducted in India. Details can be had from the Secretary, Indian Association for Chest Diseases, Silver Jubilee TB Hospital, Kingsway, Delhi-9 by 31.7.1969.

#### **Indian Academy of Medical Sciences**

The Indian Academy of Medical Sciences has been conducting postgraduate examinations

in different disciplines of Medical sciences on an All India basis with a view to admit candidates to the Membership of the Academy. The next examination will be held in July, 1969 in Delhi only. Application forms can be obtained from the Executive Director, Indian Academy of Medical Sciences, C-II/2, Medical Institute Campus, Ansari Nagar, New Delhi-16.

In another announcement, the Academy has also invited young scientists engaged in bio-medical research to participate in the Scientific session of its annual meeting to be held in December, 1969 and is open to scientists of the age of forty and below. Selected scientists will be paid travelling and daily allowances for attending the Scientific session of the Academy and for presenting their papers. The papers should be submitted to the Executive Director not later than 15th September, 1969.

### **MINER'S DEATH CAUSED BY INH OVERDOSE**

A FREAK accident, which resulted in the death of one African miner and the poisoning of 199 others, occurred at the Doornfontein Gold Mine, near Carletonville, early in November.

Instead of the usual purgative administered at their dressing stations they received, in error, doses of isoniazid or INH, the well-known effective drug used in TB treatment, which in therapeutic doses is harmless. They developed stomach cramps and started vomiting and were taken to hospital where one of them died later in the day. The others recovered.

The mine concerned is one of those which has in the past six years been adding, with the consent of the mine workers, prophylactic INH to their daily ration of marewu, a non-alcoholic maize drink popular among Africans. This experimental scheme, reported in SANTA News (September, 1968) has shown an 80 per cent decrease in TB incidence among the 41,000 African miners who have taken part.

*From SANTA NEWS, December, 1968*

## UPHILL ANTI-T.B. FIGHT

A CERTAIN COMPLACENCY is discernible of late in the public attitude to such dread scourges as tuberculosis. The development of powerful anti-microbial drugs and the perfecting of effective and yet comparatively low-cost domiciliary treatment for sufferers from this disease (as against the expensive medical care in sanatoria) may have something to do with it. But the figures of the high incidence of this killer (7 to 8 million cases) and deaths (half a million) from it every year and the inadequate facilities for its control available, referred to by Dr. S. Chandrasekhar, Union Minister of State for Health, at the 30th annual meeting of the Tuberculosis Association of India should serve to warn against any relaxation in the war on this old and insidious enemy. The plan of attack leans heavily on having at least one Control Centre in each district from which radiate teams to diagnose and treat the victims in the area. Only 171 of the 336 districts in India have such centres and each of these control points can deal with only about 4,000 cases. The inexorable arithmetic of it all is that as many as 5 to 6 million T.B sufferers go without proper medical help. And coming from the Union Minister of Health himself, this confession of inadequacy is indeed as alarming as it is authentic.

The obvious remedy is to quicken the tempo of enlargement of the clinics and control centres. But the hurdles that have slowed down the process in the past—lack of trained workers, funds, equipment and so on—are still there. Fortunately, the voluntary T.B. Association of India has a wider network of district branches, covering 207, than the official agency. Between these branches and private doctors, the general practitioners practising in the area, much may be done to fill the gap in more organised facilities. Dr. P.K. Duraiswami, Chairman of the Association, has suggested the strengthening of the curriculum of medical under-graduates, to include more expertise on the treatment of this disease to help even G. Ps. to tackle T.B. patients with competence. Even as it is, if every general practitioner refers suspected cases to the nearest clinic and undertakes the supervision of the follow-up treatment and the education of their contacts, they would be supplementing the organised network of control centres. The Association which has been doing yeoman service to publicise the perils of T.B. and harness public opinion to fight it may add more sinews to its programme, if it can enlist both women's organisations and the private medical practitioners in its work to a much larger extent than now.

*(Editorial in Hindu of April 21, 1969)*

# The Indian Journal of Tuberculosis

## ABSTRACTS

Vol. XVI

April 1969

Abst. No. 2

### **Sensitivity to Thiacetazone of Myco-Bacterium Tuberculosis Isolated in Algiers Practical Deductions;**

*J. Grosset; F. Rodriguez; M. Benhassine, P. Ghault and D. Larbaoui, Tubercle, Supplement, Vol. 49, March, 1968.*

There is, no correlation between 'natural' sensitivity to thiacetazone and 'natural' sensitivity to ethionamide. However there is Correlation between acquired resistance to ethionamide and resistance to thiacetazone. There is however systematic cross resistance between the two drugs.

H.B.D.

### **Natural Sensitivity of M. Tuberculosis to Thiacetazone.**

*D.A. Mitchison, Tubercle, Supplement, Vol 49 March 1968.*

1. Efficacy of thiacetazone plus isoniazid varies from one area of the world to another.
2. Preliminary control trials should be carried out when the use of this combination is envisaged on a major scale.
3. There is no association between the results of pretreatment thiacetazone sensitivity tests and the response to treatment.
4. The routine use of such sensitivity test is un-necessary when this combination is widely used.

H.B.D.

### **Tuberculin Test in Children with Malnutrition**

*Aune V.C. Lloyd, Brit Med. Jur. 31st Aug. 1968.*

In 402 children with severe malnutrition, Tuberculin test with Heaf's multiple puncture method as well as intradermal test with varying strength of old tuberculin were carried out

Of these 402 children, active tuberculosis was in 51 (12.5%) as shown radiologically and bacteriologically.

The Heaf test was positive in only 11 of these children and the intradermal test using 100 tuberculin units was positive in a further 18 children. This confirms previous findings that tuberculin sensitivity is impaired in malnourished children and suggest that a higher dose of tuberculin is more likely to elicit a positive response.

H.B.D.

### **Streptomycin Plus Thiacetazone (Thioacetazone) Compared with Streptomycin Plus P.A.S. and with Isoniazid Plus Thiacetazone in the Treatment of Pulmonary Tuberculosis in Rhodesia.**

*L. Briggs et-al. R. W. Raddle, and Wallace Fox et-al. Tubercle, Land. (1968), 49, 48.*

220 patients were allocated at random to three treatment regimens.

*T.H.*

Thiacetazone 150 mgm plus isoniazid 300 mgm daily in a single tablet.

*S.P.*

Streptomycin sulphate 1 gm intramuscularly plus sodium PAS 15 Gm. daily in three doses.

*S.T.*

Streptomycin sulphate 1 gm. intra muscularly plus thiacetazone 150 mgm daily in a single tablet. All patients were treated in hospital for six months. There were 171 (58 TH, 55 SP, 58 ST) patients who complied with clinical criteria for admission and who had strains of tubercle bacilli sensitive to isoniazid and streptomycin. Ten patients died, five (two SH, two SP, one ST) from active tuberculosis, three (one SP, two ST) from non tuberculous causes but with active tuberculosis and two

(both TH) from possible drug toxicity with active tuberculosis. The sputum was negative on both cultures at six months in 72% of TH, 82% of the SP and 33% of the ST patients. At three months none (0%) of the 53 SP and 20 (37%) of the 54 ST patients were excreting streptomycin resistant organism ( $P < 0.001$ ). At six months isoniazid resistant strains were obtained from 13% of 54 TH patients and 8% of 53 SP patients had culture with an RR of 4 or more of P.A.S.

At six months 72% of 58 TH, 76% of 55 SP and 26% of 57 ST patients had favourable response classified mainly on bacteriological grounds. The difference between the ST and each of the other two regimens were statistically highly significant ( $P > 0.0001$ ). Cutaneous hyper sensitivity occurred in 9% of the TH, of 10% of the SP and 10% of the ST patients. It was most severe in TH patients. Jaundice occurred in one patient in each of the three series and dizziness was recorded only in the ST patients, occurring in 11%.

It is concluded that ST regimen was markedly inferior. The SP and TH regimens were of similar effectiveness, the latter being an effective oral regimen.

H.B.D.

#### **Aspergillus in Persistent Lung Cavities After Tuberculosis**

*A report from the Research Committee of the British Tuberculosis Association, Tubercle, Lond., (1968), 49, 1.*

Of 544 patients with persistent cavities of 2.5 Cm. or more in diameter, 134 (25%) had a positive precipitin test. In 59 (11%) radiographs showed typical appearances compatible with a aspergilloma and precipitin. A further 19 (4%) had less typical but highly suggestive appearances and precipitines. In most of these the precipitine test was strongly positive whilst the result was weaker in those without such radiographic evidence. The maximum prevalence of aspergillus infections occurred in those with cavitated tuberculosis of seven to 11 years duration and it became constant at a somewhat lower level in those with longer standing disease.

The affected patients had larger cavities and cavities with thicker walls showed more pleural thickening and had more cough and were frequent recent haemoptysis. Five patients (1%) without precipitins were found to have radiographs typical of a mycetoma,

H.B.D.

#### **Blood Levels of Isoniazid and of Its Methane Sulphonate Derivative in Rapid and Slow Inactivators After Oral Administration.**

*Aldo Baronti and Nella Manfredi, Tubercle, Lond., (1968), 49, 104.*

Blood levels after oral administration of isoniazid and its methane sulphonate derivative (Methaniazid) were compared in a group of 20 subjects consisting of 10 rapid and 10 slow inactivators.

The two drugs were administered orally at a dose of 5 mgm/Kgm calculated as isoniazid, blood samples were drawn at three, six and nine hours and assayed with the vertical diffusion method using *Mycobacterium Tuberculosis* H 37 R as test organism.

The blood levels reached after administration of methaniazid were significantly higher than those obtained with isoniazid ( $PL < 0.001$ ) in slow inactivators the difference of blood levels obtained with two drugs did not reach a significant level ( $0.10 > P 70.05$ ).

H.B.D.

#### **Ethambutol Treatment of Tuberculosis in a Controlled Trial**

*Francis O. Segatra, Victor Lorian and David S. Sherman Scand. J. Resp. Dis : 493, 202.*

The efficiency of ethambutol in combination with INH and PAS in previously untreated cases has been evaluated in a controlled trial. After excluding those who did not complete 3 months' treatment, there were 47 patients in the ethambutol group and 20 in the control group. Nearly 10% of the strains isolated from each group of the patients showed primary resistance. The relief from clinical symptoms, radiological change and sputum conversion was marginally better in the control group. Further, the patients in the control group achieved conversion in less time than the patients in the ethambutol group. One patient in the 20 in the control group developed acquired resistance to INH as compared with 9 of the 47 in the ethambutol group.

Three patients in the control group developed severe intolerance to PAS and had to be withdrawn from the study as against only one patient who developed jaundice in the 3rd week of treatment in the ethambutol group and had to be withdrawn. No visual disturbances were observed.

S.P.P.

**Ethambutol in Initial Treatment**

*Adil Sokmensuer, Transactions of the 27th VA-Armed Forces, Pulmonary Diseases Research Conference ; 1968, 3.*

Twenty three hospitals in United States co-operated to determine the effectiveness as well as the toxicity of ethambutol as a substitute for PAS in initial treatment of pulmonary tuberculosis. Some of the patients included in the study in the beginning were given 6 mg per kg. of ethambutol but subsequently the dose was increased to 15 mg per kg. body weight. INH with low dose ethambutol was as effective as INH and PAS in reversing infectiousness for the first 12 weeks, but thereafter some patients in the former group showed bacteriological reversions. In the case of high dose ethambutol group, sputum conversion throughout the trial period was equal to INH-PAS group and the bacilli in no case developed resistance to INH. Adverse reactions severe enough to warrant withdrawal from the drug schedule used, were seven times more with PAS than with ethambutol.

S.P.P.

**Ethambutol in the Re-treatment of Pulmonary Tuberculosis**

*Hugh Kelly, Transactions of the 27th VA-Armed Forces, Pulmonary Diseases Research Conference ; 1968, 4.*

Nineteen hospitals in United States participated in a trial to test the effectiveness of ethambutol used in triple drug combination for re-treatment of pulmonary tuberculosis. All patients had received antimicrobial treatment for at least 6 months prior to this trial. The drug regimens were used comprising of INH and various combinations of the second line drugs. Nine of the ten regimens included ethambutol also. Two hundred and seventy seven patients completed the treatment for a stipulated period of 16 weeks. Eighty five percent of these patients were excreting bacilli resistant to INH. The sputum conversion rate was 75%- The conversion rate showed no significant difference in the various regimens. Severe intolerance to ethambutol warranting withdrawal of the drug appeared in 6 out of 203 patients receiving this drug. Capreomycin was given to 44 patients, and none of these had any severe reaction. The toxic reactions to the other second line drugs used in the trial were fairly frequent. Ethionamide had to be withdrawn in 13% and cycloserine in 26%.

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The decrease in visual acuity was no more in patients treated with ethambutol than in others.

S.P.P.

**Ethambutol and Visual Acuity**

*Rae S. Newman, Transactions of the 27th VA-Armed Forces, Pulmonary Diseases Research Conference; 1968, 4.*

The visual acuity in 2 groups of patients, one given a dose of ethambutol 6 mg per kg. and the other 16 mg per kg. body weight has been compared in 1,219 patients. The decrease in visual acuity was no more frequent in high dose group than in the low dose group.

S.P.P.

**The combined use of capreomycin and ethambutol in re-treatment of pulmonary tuberculosis**

*Imasato Donomae: Amer. Rev. Resp. Dis.; 1968, 98,699.*

Capreomycin and ethambutol were given for one year to 89 patients who underwent re-treatment for cavitary pulmonary tuberculosis and were excreting bacilli resistant to the standard drugs. At 6 months, the cultures were negative in 75% whereas in the remaining 25% a gradual increase in the incidence of resistant strains was seen with continuation of treatment.

Side effects of capreomycin viz difficulty in hearing, tinnitus and injection pain were reported by 7 patients though the symptoms were severe enough to require withdrawal of drug in 3 cases only. The decline in visual acuity, abnormality in visual fields and eye strain occurred in 6 patients but ethambutol had to be withdrawn only in one case.

Because of sclerotic nature of the lesion, radiological regression of lesions was observed in 27.7% of the patients at 12 months. Slight to moderate decrease in the size of the cavity was noticed in 36.3% of the patients. Closure of cavities was obtained in 13.7% at 12 months treatment.

S.P.P.

**The antimicrobial activity of Rifampin**

*Gladys L. Hobby, Tulita F. Lenert. Amer. Rev. Resp. Dis., 1968, 97, 713.*

A series of experiments were performed to compare the *in vitro* and *in vivo* activity of

rifampin with that of INH. The data suggest that rifampin is approximately one half as active as INH against INH-sensitive strains, both *in vitro* and *in vivo*, but is active at least *in vitro* against INH-resistant strains.

S.P.P.

### Re-treatment of patients with isoniazid-resistant tuberculosis

*D.A. Fischer, William Lester, William E. Dye and Thomas S. Moulding. Amer. Rev. Resp. Dis.; 1968, 97, 392.*

The results of treatment with various combinations of second line drugs and follow up in 146 patients with INH resistant bacilli have been analysed. All patients were treated from 1960 to 1962, with a medium duration of 46 months follow up. After 120 days of treatment, the sputum of 122 (83.5%) became negative. The median time for conversion was 47th day of chemotherapy. There were 27 deaths up to January, 1966 and there were only 7 survivors who failed to respond to treatment. Thirty patients (20.5%) experienced bacteriological relapse during the period of observation. Relapse occurred at a median time of 12 months after start of treatment. Significant toxic reactions were encountered in 42% of the patients and appeared after a median duration of more than 60 days of treatment with any specific drug. Of the surviving patients whose status was known in January 1966, 88% remained consistently non-infectious.

S.P.P.

### The Problem of the Chronic Excretor of Tubercle Bacilli

*K. Styblo, A. Kubik, M. Langerova, E. Muthu Skova and K. Moravkova. Scand. J. Resp. Dis.; 1968, 49:3, 236.*

The management of chronic excretors of tubercle bacilli in the district of Kolin, Czechoslovakia, with a population of 100,000 has been studied. A person who had been excreting tubercle bacilli persistently for a period of 2 years or more was defined as 'chronic excretor'. There were 53 such patients on 1st October, 1960 when the study started and 16 more patients qualifying for the definition were added up to the end of the study on 31st March, 1967.

All these patients were kept in the hospital for 9 to 15 months, followed by ambulatory

chemotherapy. The total duration of treatment was at least 18 months. Three drugs were used during the stay in the hospital, one of which was INH, streptomycin ethionamide or pyrazinamide but the bacilli had to be fully sensitive against all drugs used. During the ambulatory treatment, only two drugs were used.

Sensitivity tests were available for 56 patients, out of which 48 were resistant to one or two of the 3 standard drugs (viz INH streptomycin and PAS) and 8 were resistant to all three. Total cases resistant to INH were 45, to streptomycin 28 and to PAS 19. Of the 45 strains resistant to INH, 15 were fully virulent and in the remaining 30, the virulence was attenuated.

Out of the 69 chronic excretors, only 62 took drugs over 3 months. Of the remaining 7, 4 died from a serious concurrent disease and 3 died from Tuberculosis within 3 months. There were 25 more deaths up to the end of the study. Of the 37 patients surviving on 31st March, 1967, 32 were converted and only 5 were still infectious. If deaths after 3 months are included, the sputum conversion was obtained in 66%. Out of the 25 deaths amongst those who had been treated for more than 3 months, 9 were converted at the time of death.

There were 104 family contacts, of these 69 chronic excretors and they were also kept under surveillance. Two children, both BCG vaccinated earlier, developed bacillary disease during the period of observation. In one of them the bacilli were resistant to INH and in the second the bacilli were sensitive to all three drugs. None of the contacts over the age of 15 developed tuberculosis. Although the role of these chronic excretors in the dissemination of infection among general population cannot be estimated, the authors are of the opinion that they did not influence the incidence of primary drug resistance in subsequent years in the community to any appreciable extent.

S.P.P.

### Primary Tuberculosis in Children

*Morris Steiner, Raymond Zimmerman, Byung Hak Park, Sudheer R. Shirall and Harry Schmidt. Amer. Rev. Resp. Dis.; 1968, 98, 201.*

Of the 52 strains of M. Tuberculosis isolated from children with primary disease, 3 strains were significantly resistant to INH and 3 to streptomycin. The same prevalence of

drug resistant strains was found in strains isolated from the corresponding source cases.

All 137 strains of *M. Tuberculosis* isolated from all children, 9 were significantly resistant to INH compared with 6 of the 79 strains from the source cases. The prevalence of streptomycin and PAS resistant strains was also similar. The study indicates that the level of primary drug resistant infections among children in the community under surveillance is closely comparable to the level of drug resistance among the adults<sup>77</sup> from whom the tuberculosis infection is acquired.

S.P.P.

### Spread of drug-resistant tubercle bacilli

*E. Brander, K. Aho & J. Patiala. Amer. Rev. Resp. Dis.; 1968, 98, 407.*

The source infection was studied in 50 adult cases of pulmonary tuberculosis caused by primarily drug-resistant bacilli of human type. The patients were relatively young, with a medium age of 25 years as compared to 41 years in the case of all newly diagnosed cases. Seven of the strains were resistant to all the three major drugs, 3 to two drugs and the remaining 40 to one drug only. With the exception of two catalase—negative strains, the bacilli gave rise to progressive disease in the guinea pigs.

A positive source of infection was found in 7 of the 11 patients more than 45 years old. Only 3 of the 23 patients less than 25 years of age disclosed a possible source of infection whereas 13 gave the history of old contact.

The results indicated that the disease in the majority of the young patients originated from the old primary infection caused by drug resistant bacilli. The study also demonstrates usefulness of drug resistance as a microbial marker in the epidemiological study of tuberculosis.

S.P.P.

### Effect of ultra violet irradiation on the acid fastness of drug-resistant mutants of tubercle with special reference to the virulence of isoniazid-resistant strains

*Toyoho Murohashi and Konosuke Yoshida. Amer. Rev. Resp. Dis.; 1968, 97, 283.*

There is a high degree of co-relation between the degree of INH resistance, the virulence of the resistant bacilli and the effect of ultra violet irradiation effect on acid-fastness by a much shorter period of ultra violet irradiation than the virulent strains and their streptomycin and PAS resistant mutants. The factor that is suspected to be concerned appears to be the cell wall structure of the bacillus which becomes thinner in accordance with the degree of resistance to INH.

S.P.P.

### Pseudocavities of the Lung

*Sanford E. Rabushka & Hiram T. Langston. Amer. Rev. Resp. Dis.; 1968, 97, 644.*

The concept of pseudocavities in the lung has been discussed. The high lipid content of caseous material in the centre of round foci often gives a shadow, indistinguishable radiologically from the shadow of a real cavity. This concept has been proved through radiological studies with 'mock' lesions attached to the chest of volunteers before radiography.

S.P.P.

### Singing and the Dissemination of tuberculosis

*Robert G. London. Rena Marie Roberts, Amar. Rev. Resp. Dis.; 1968, 98, 297.*

The risk of droplet infection through singing has been studied. Fewer droplets were expelled during singing than during talking, but a higher proportion of them were in the smaller size range. The percentage of droplets still airborne as droplet nuclei after a 30, minute settling period were 35.7, 6.4 and 48.9 for singing, talking and coughing respectively. The very high proportion of smaller droplets expelled during singing would tend to indicate high risk of infection through this means.

S.P.P.