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MEDICAL RESEARCH AND TUBERCULOSIS

When thinking of medical research, one has a tendency to imagine the existence of a laboratory with test tubes, chemical reagents, microscopes, animals for experimentation, etc. These are doubtless necessary components of medical research. But there is also the need to test out in human beings the results of laboratory experiments. The new anti-bacterial drugs now widely advocated and used for tuberculosis were first tested in laboratories and on animals before they came to be used on patients and their usefulness confirmed. The human part of the experiment is usually done in a limited number of patients and that in institutions under close supervision. It is not enough to confirm that a line of treatment is useful, it is also necessary to find out the efficacy of both preventive and curative methods when used on a large scale in the community. This is particularly needed in a disease like tuberculosis with protein manifestations, and which sometimes takes long to develop and long to cure. A good deal of research and investigation are therefore needed in the community as different from these in laboratories and institutions. In India at present, and also in other developing countries, the tuberculosis problem is large and serious and they need the results of such investigations to help in planning anti-tuberculosis measures in a practical way so as to achieve the maximum results in the shortest time possible. The Indian Council of Medical Research has been, in recent years, developing certain research projects with this end in view.

One of the projects it has undertaken in this respect was the National Sample Survey on Tuberculosis in 1955, the results of which were published in 1958. Another important research is that

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of Chemotherapy in Tuberculosis in Madras with the active cooperation of the World Health Organisation and the British Medical Research Council. Many papers giving the results of investigations in this centre on various aspects of domiciliary treatment have already been published and several are in the process of being published.

Another research project is the Madanapalle Field Research. This was started on a small scale with limited objectives in 1948 but later expanded to cover a population of over 200 thousand including rural and urban population within a radius of 100 miles from the centre. Various papers and reports from this centre were published during the last ten years and some of these were given in this journal. The main object of this research at present is to find out the success or otherwise of self-administration of anti-tuberculosis drugs in the community control of tuberculosis using the minimum supervision.

The new National Tuberculosis Institute at Bangalore under the Government of India is also engaged in investigations and research but of somewhat different nature. They are finding out the efficacy of different approaches to tuberculosis control work. In this they are proceeding on the knowledge gained at the two Centres mentioned earlier but making use of village and other workers associated with public health departments of the States, community development blocks, Panchayats and voluntary organisations, in carrying out these methods. They include in their investigations sociological problems in the community that influence the spread of tuberculosis and the acceptability of treatment etc.

Another problem that is being investigated under the auspices of the I.C.M.R. is the assessment of the results of BCG vaccination in India by a specially trained team, in different groups of population, in various parts of the country, who have had BCG vaccination since 1952.

Though all these projects have the main objective of finding out the best way to control tuberculosis in a community, yet they vary in some respects, as each concentrates on a different facet of the problem. However, they are all coordinated by the TB

Section of the Central Health Ministry, to avoid overlapping and duplication.

While the above gives a bird's eye view of the more important Tuberculosis Research Schemes that are in progress in the country, we cannot ignore the fact that there are some who are not convinced of the need for these research projects. Some are impatient of not getting quick results; many do not understand the need for long term planning and providing adequate finances; some others do not realise the importance of securing research workers of high calibre and providing them with conditions necessary to keep them in the line, once they take to it. But fortunately there are many who can appreciate the importance and implication of this type of community research in tuberculosis. India is in the throes of planning and in this they emphasise the need for long-term planning. If this policy is followed in medical research also, we may reasonably hope to find some solution for the many problems connected with the control of tuberculosis in India.

Aetiology of Tropical Eosinophilia ‡

By

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As members of this Association are very well aware Dr. Frimodt-Moller and Mr. Barton were the first workers to describe a significant number of cases of tropical eosinophilia (TE) in India. Since 1940 when their report was published, this disease has been recognised as common throughout India and there has been much speculation regarding its causation. Various theories have been advanced including allergy, and infection with viruses and with mites. However no good and consistent evidence has been produced in support of any of these theories. Gradually over recent years evidence has accumulated, pointing to some form of filarial infection as the cause. This evidence derives from four distinct approaches to the problem.

The first form of evidence which relates unequivocally to forms of the disease familiar in India has been the prompt therapeutic response to the antifilarial drug diethylcarbamazine. Some of the first workers to demonstrate the effectiveness of this drug in India were Ganatra and Lewis. Since then a number of careful studies in India and Malaya have confirmed that almost all cases diagnosed as TE respond promptly to diethylcarbamazine. Danaraj in Malaya has found it consistently true with all his cases.

The second form of evidence, again developed by Danaraj in Malaya, has been the demonstration in almost all cases of TE of complement fixing antibodies in the serum against a filarial antigen made from *Dirofilaria immitis* (FCFT). Danaraj found only ten negative sera in 213 cases of TE, positive titres ranging from 1 : 5 to 1 : 320, and the mean being 1 : 40.

A third form of evidence has been the demonstration of microfilariae in the lymph-nodes of cases presenting with lymphadenopathy and massive eosinophilia in the blood. Meyers and Kouwenaar were responsible for one of the first reports of this kind. They demonstrated microfilariae in sections of lymph-nodes removed from Javanese patients. Similar reports have come from Van der Sar and Hartz who described four similar cases in the West Indies, and more recently French workers have seen a similar disease in French soldiers who had served in North Vietnam. In this particular form of the disease the presenting symptom has usually been a fairly marked lymph-node enlargement. Since lymphadenopathy has not generally been regarded as a feature of TE, it is probable that this syndrome has not been identified in most people's minds in India with the TE we encounter here.

The fourth form of evidence has been provided by some experiments conducted by Professor Buckley of the London School of Hygiene and Tropical Medicine. Buckley was primarily interested in determining whether filariae infecting various common animals in Malaya are infective for men. Infective larvae were dissected out of mosquitoes which had fed on an infected monkey, and injected into a volunteer. The blood of the volunteer was examined daily for microfilariae with regular eosinophil counts. He

‡Paper presented at the XVII All India Tuberculosis Chest Diseases Workers Conference held at Cuttack in Jan. 1961.

never developed microfilaraemia, but after fourteen weeks his eosinophil count rose to levels similar to those encountered in TE and he developed cough and a certain amount of wheezing. His FCFT also rose. Symptoms subsided gradually without specific treatment and after a period of several months the same volunteer was infected with larvae obtained from mosquitoes which had fed on a cat infected with *W. pahangi*. Ten weeks after the second infection the volunteer developed a very high eosinophilia with acute respiratory symptoms for which he had to be admitted to hospital and treated with oxygen. Similarly the FCFT rose to a titre of 1 : 640. Symptoms subsided very rapidly when he was treated with diethylcarbamazine.

In 1952, Beaver and others were able to demonstrate that infection with *Toxocara canis* was the cause of a syndrome encountered in young children in the Southern United States, and marked by hepatomegaly, pulmonary infiltration and massive eosinophilia. They called this disease visceral larva migrans. They showed that the children became infected by eating garden soil containing embryonated ova of the dog ascaris. The larvae from these migrated from the gut via the portal circulation to the liver. Instead of passing through the liver to the lung and back to the intestine, the organisms became trapped in the liver where they excited an eosinophil granulomatous reaction. A few organisms passed through the liver, the majority evidently dying in that organ. This vigorous reaction to the invading larvae was clearly responsible for the hepatomegaly, the eosinophilia, and all the essential features of the disease. In discussing this disease Beaver and his colleagues postulated that a similar mechanism of zoonotic helminthic infection might be the cause of eosinophilias encountered in other parts of the world. Specifically, they suggested that such a mechanism might be the cause of TE in Asia.

It was this suggestion of Beaver and his colleagues which led us at Vellore some four years ago, to initiate an investigation into the aetiology of TE. This has been a joint study by the department of Pathology and Pediatrics. The primary object was to obtain tissues from typical cases of TE and to study these tissues for the possible presence of parasites.

Clinico-pathological investigation

From among children presenting with the accepted features of TE, which ordinarily included an absolute eosinophil count of at least 4000 per cmm, a positive FCFT and a therapeutic response to diethylcarbamazine, cases were selected for tissue biopsy.

Initially, interest was focussed on the liver. After a series of needle biopsies had revealed nothing beyond eosinophil infiltration of portal tracts, open liver biopsy was performed in five typical cases. Subsequently, lymph-node biopsy was performed in three children presenting with lymphadenopathy incidental to a typical respiratory syndrome. Throughout the period of investigation, every opportunity was taken to study lung tissue. One adult, a man of 22 years, required pneumonectomy for a tension cyst. One child had lung tissue taken for biopsy at the time of ligation of a patent ductus arteriosus. One boy was admitted specifically for lung biopsy, and one lung which had been resected in 1950 for supposed lung abscess, found later to be an eosinophil granuloma, was available in formalin for histology.

All tissues obtained in this way were processed routinely for histology and sectioned serially at seven microns, the whole of each section being searched under the high power (magnification X 450) for organisms. Some 10,000 sections were searched and in some instances re-searched in this way.

Lung-Lesions

The material was ideal for pathological study. The tissue before dissection was soft and spongy with nodules 3-5 mm in diameter scattered irregularly over the cut

surfaces. Microscopically the lung architecture was well preserved, apart from the scattered nodules. These nodules consisted of groups of alveoli containing fibrin and eosinophils. In some nodules the alveolar walls were preserved but there was some oedema and eosinophil infiltration. In other nodules, evidently more mature, alveolar walls had disappeared with the formation of a granuloma. A number of granulomata contained eosinophilic necrotic material in the centre. The appearance of this material was at times very similar to that described by Meyers and Kouwenaar and now often referred to as the Meyers-Kouwenaar (MK) bodies. In other granulomata portions of larvae were identifiable. In nodules where no larvae were found foreign body-type giant cells were sometimes present, and in these there might be some scanty peripheral fibrosis.

In the 5,000 lung sections examined, five almost complete microfilariae were found. Slides containing two of these were sent to Professor P. C. Beaver, Professor of Parasitology in the University of Tulane, Louisiana. He confirmed the identification of these organisms as microfilariae but was unable to determine the species.

Liver Lesions

In all the cases where laparotomy was performed, the liver was slightly enlarged and the surface was studded with a variable number of white dots 2-5 mm in diameter and varying in number from 4 or 5 to hundreds. On microscopic examination, these nodules were found to be eosinophil granulomata essentially similar to those encountered in the lung. MK bodies were found in several of these and in one case an almost complete microfilaria, identified as such by Professor Beaver, was found.

Lymph-node Lesions

Lymph-nodes removed for biopsy were divided, part of the tissue being fixed in formalin and processed routinely for histology and part being teased in saline. These saline preparations were allowed to stand at room temperature for several hours and then centrifuged. In some cases wet preparations of the deposit contained live microfilariae. Serial sections for histology showed typical eosinophil aggregates and granulomata in a number of which microfilariae were identified.

DISCUSSION

The basic pathological lesion of TE common to all tissues involved has been shown to be an eosinophil granuloma. The demonstration of microfilariae in the centre of typical lesions in the lung of four cases leaves little room for doubt regarding the causative role of these organisms. Even though parasites have been demonstrated in only a small proportion of all the nodules studied, it seems reasonable to assume that nodules represent a direct reaction to an invading organism and not a reaction to some remote allergen. Obviously some evidence of tissue reaction can be expected to persist long after the exciting parasite has died and disappeared beyond recognition or identification.

The demonstration of microfilariae in similar nodules in the liver and lymph-nodes of typical pulmonary cases shows that these organs too may be involved in TE. Experience at Vellore suggests that this involvement of liver and *lymph-nodes* is more likely to be seen in young children than in adults.

Apart from the typical cases of TE presenting with respiratory signs and symptoms, we have encountered cases with *lymph-nodes*, but no lung involvement, with liver and *lymph-node* but no lung involvement and apparently with isolated involvement of the liver. Such cases would not ordinarily be regarded as examples of TE. However, all

these cases share the essential features of an eosinophil granulomatous reaction in the tissues involved, the presence of microfilariae demonstrable in the centre of some of such lesions, a massive eosinophilia in the blood, a positive FCFT and a therapeutic response to diethylcarbamazine. It would therefore seem wise to enlarge the concept of TE to embrace all these clinical profiles. At the same time we would like to see the term restricted to those cases in which a filarial infection is suspected or proved. Visceral larva migrans is an example of an eosinophilia where the etiology is quite distinct from that of TE. It is likely that other parasitic infections may at times produce eosinophilia, of the same order as that encountered in TE in India. We would like to see new names⁷ introduced for such diseases as and when distinct infections are identified as their cause. It appears to us to be misleading to call infections with *Toxocara canis* examples of TE whether this disease is induced in Calcutta or seen occurring naturally in New Orleans, it is visceral larva migrans.

The presence of microfilariae in lung, liver and lymph-nodes implies two things. First, infective larvae introduced by mosquito bite must have matured somewhere in the body to adult filariae capable of reproduction. Secondly, microfilariae released from adult females are being disseminated through the body, becoming trapped in different tissues where they excite a characteristic eosinophil and later granulomatous reaction. Although the dissemination of microfilariae is almost certainly haematogenous this must be reconciled with the consistent failure to demonstrate microfilaraemia in any case of TE. This has been our experience at Vellore and this has been the experience also of Danaraj in Malaya. The explanation may be that the microfilariae after release into the circulation, are trapped in the first set of capillaries through which they pass. This will normally be in the lung which would account for the predominance of pulmonary involvement in this disease.

That TE as encountered in India is normally due to some form of filarial infection now appears proved beyond any reasonable doubt. However, certain important questions remain unanswered. Why does filarial infection in some people cause TE, while in others the infection may be present for years with very little tissue reaction apart from occasional lymphadenitis and lymphangitis. Why is microfilaraemia constantly present in typical filariasis, at least until relatively late in the disease, and why is microfilaraemia never encountered in TE. The most reasonable and readily acceptable explanation at present available is that postulated by Beaver and apparently so dramatically vindicated by Buckley's experiments. An animal filarial infection might be expected to cause a different type of tissue reaction from that seen with filariae normally parasitic in man. It was our hope that a specific identification of the microfilariae found in tissues would be possible and that in this way this question might be resolved, but this hope has not been realised. However, microfilariae obtained from lymph-nodes have been identifiable in stained preparations and all those examined have been indistinguishable from *W. bancrofti*. This at first sight seems to make an animal filarial infection unlikely. However this is not necessarily the case. Edeson, Wharton and Buckley reported the recovery of sheathed microfilariae indistinguishable from human *W. malayi* from five different species of animal in Malaya. Further observation on the life-cycles of these microfilariae revealed that there were at least two species of filaria involved. It is possible that similar animal filariae are present in India and that the microfilariae of these parasites are morphologically indistinguishable from those of *W. bancrofti*. This at present is mere speculation but for the time being the hypothesis of zoonotic filarial infection as the cause of TE appears to be the most acceptable.

SUMMARY

1. The pathological changes in the lung, liver and lymph-nodes of typical cases of tropical pulmonary eosinophilia are described.

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2. Microfilariae have been demonstrated in the centre of nodules in each of these tissues, suggesting that direct invasion by these organisms is the cause of the lesion in this disease.

3. Cases have been encountered with lymph-node and hepatic, but without lung involvement. The lesions in these cases are similar to those seen in the lung, and microfilariae are present. A plea is made to enlarge the concept of tropical eosinophilia to include such cases, and at the same time restrict it to those in which a filarial infection is proved or suspected.

4. Microfilariae recovered from lymph-nodes have been provisionally identified as *W. bancrofti*-type, but on the analogy of findings in Malaya, it is suggested that these may be of animal origin and that zoonotic filariasis remains the most likely explanation of tropical eosinophilia.

Progress in the Second Year of Patients with Pulmonary Tuberculosis after a Year of Chemotherapy at home or in Sanatorium and Influence of further Chemotherapy on the Relapse Rate. *

By

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It was reported recently from the Tuberculosis Chemotherapy Centre, Madras (1959) that a controlled comparison of combined chemotherapy with Para-aminosalicylic acid and Isonicotinic acid hydrazide among South Indian patients showed that response of one year's domiciliary treatment closely approached the results of sanatorium treatment. All these patients belonged to the poor urban community in Madras City and were living under unfavourable domiciliary conditions. 126 patients who had attained bacteriological quiescence at the end of one year were followed up in the second year for a further period of 12 months. A great majority of these patients followed their usual occupation while undergoing treatment. They were the subjects of a controlled study of long-term chemotherapy based on random allocation. They had no surgery or any other antituberculosis measure as an adjunct to chemotherapy and all received their treatment on a domiciliary basis.

The main objects of this follow-up study were to determine:

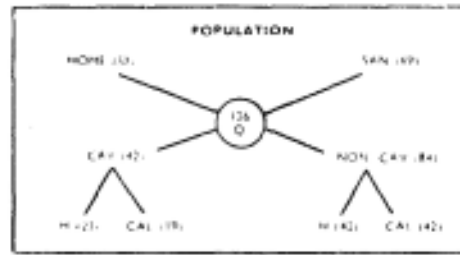
- (1) whether relapse in the second year was more frequent among patients originally treated at home than among those originally treated in the sanatorium,
- (2) whether the second year antituberculosis chemotherapy with isoniazid alone would reduce the relapse rate, and
- (3) the influence of residual cavitation at one year on the results of the second year treatment.

Population Studied

Table 1 describes the population studied. At the end of one year 57 patients from the home series and 69 from the sanatorium series had attained bacteriological quiescence. Of the 126, 42 had residual cavitation and 84 showed no residual cavitation. By a process of random allocation 65 patients were given isoniazid and 61 calcium gluconate as treatment in the second year.

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TABLE I



Procedures

In the second year patients attended the Centre once a month for collecting their supply of medicaments and for routine examinations. Their homes were usually visited twice a month by a health visitor, one planned visit to deliver a bottle for a sputum specimen and the other, a surprise visit, to count the stock of isoniazid pills and collect specimens of urine. Frequently these patients were not at home when the health visitor visited because they had gone out to work.

Monthly investigations and assessments undertaken at the clinic included:

- (a) A postero-anterior radiograph (large film).
- (b) an examination by smear and culture of an overnight sputum specimen, or, if the patient had no sputum, by culture of a pair of laryngeal swabs.
- (c) Tests of sensitivity to isoniazid on positive cultures.
- (d) The assessment of weight in pounds.
- (e) Estimation of ESR (by Westergren—one hour reading) once every three months was the routine that was followed.
- (f) Every case at the end of the second year had a series of tomograms taken.
- (g) At the 24th month two overnight sputum specimens were examined by smear and culture and a pair of laryngeal swabs was examined by culture.

The standard procedure was to obtain 14 specimens from each patient during the second year for bacteriological examination. It was observed that on an average 13.4 cultures were examined during the second year in this group of patients, the shortfall being due to missed specimens and contaminated tests.

All the radiographic series and the tomographs were reviewed by an independent assessor who was neither aware of the place of treatment of patients in the first year nor the treatment which they received in the second year. The assessor scrutinized the films and classified the radiographic appearance according to (a) the extent of residual disease at one year on the basis of lung zone involvement, (b) the lesions as unilateral or bilateral, (c) the extent of cavitation at 1 year, (d) changes in cavitation at 2 years and (e) radiographic changes in the second year.

A close touch with the patients and their families was maintained by the Centre's staff in order to enlist their full co-operation during the second year follow-up.

Regimen of Treatment

The treatment regimens for these patients in the second year (Table II) consisted either of isoniazid alone or a placebo in the form of calcium gluconate. Allocation of treatment was done by the Centre’s statistical staff on a random basis from a series of sealed envelopes, one maintained for cavitated series and the other for non-cavitated. All the patients were treated at home in the second year and the daily dosage of drug was given in the form of a single pill to be taken in the morning. The dosage schedule of the two regimens were:

Isoniazid: 200 mg. daily, for patients weighing 100 lbs. or more;
 175 mg. daily, for patients weighing 80-99 lbs. 150 mg.
 daily, for patients weighing less than 80 lbs.

If a patient increased in weight, and moved into a higher weight category, the dosage of isoniazid was increased at the next monthly examination. If, however, the patient lost weight and moved into a lower weight category, the dosage was not lowered.

Calcium: 500 mg. of calcium gluconate a day taken as one pill in the morning.
 Isoniazid was used alone in this study for the following reasons:

1. As a reasonable maintenance therapy for patients with quiescent disease,
2. because the drug was cheaper and less bulky, and
3. because for economic reasons combined chemotherapy for 2 years was not likely to be a practicable proposition in our country.

TABLE II

Drug	Wt. of Patient in Ibs.		
	> 100	80-89	< 80
INH	200 mg	175 mg	150 rag.
Placebo	500 mg	500 mg	500 mg.
Duration of therapy— 1 Year A Single Pill Given as one Dose every Morning			
COMPARISONS			
1. Home	57	—	San 69
2. INH	65	—	Cal 61
3. Cav	42	—	Nov. Cav 84

Comparisons

Three main comparisons of the progress in the second year were made on the 126 patients on the basis of their place of treatment in the first year, cavitation status at the end of one year and the allocated treatment during the second year. They were:

1. A comparison of 57 patients who had been treated at home (referred to as "Home patients") in the first year and 69 patients who received sanatorium treatment (referred to as "Sanatorium patients").
2. A comparison of 42 patients with definite residual cavitation at one year and 84 patients without residual cavitation.
3. A comparison of 65 patients receiving isoniazid alone in the second year and 61 patients who received the placebo.

Status of Disease at the end of 1 year

The status of disease at the end of the first year's treatment of combined chemotherapy is shown in Table III. All the patients were bacteriologically quiescent and a comparison of clinical and radiographic features of home and sanatorium patients at that time showed that the home patients weighed less than sanatorium patients, had higher ESRs and rather more extensive radiographic lesions. 15 (20%) of the home compared with 44 (64%) of the sanatorium weighed 100 lbs. or more. 12% of the former had normal ESR's (10 mm. or less) compared with 38% in the latter series. Considering the radiographic features 54% of the home patients and 43% of the sanatorium patients had residual lesions in three or more lung zones; 77% of the home and 67% of the sanatorium patients had bilateral disease. 37% of the home and 30% of the sanatorium series had residual cavitation.

A comparison of the series of patients on isoniazid and those on calcium showed that the two series were similar at the start of the second year except that rather more patients in the calcium series had high ESRs. 35% in the isoniazid series and 31% in the calcium series had cavitated disease.

TABLE III

Status of Disease at one year

Patients	Home	San.	Cal.	INK.
	57	69	61	65
Wt. >100 lbs.	26%	64%	52%	42%
ESR (N)	12%	38%	20%	32%
> 3 Long Zones	54%	43%	48%	49%
Bilat. Disease	77%	67%	72%	71%
Cavitated	37%	30%	31%	35%

Status of Disease at the end of the Second Year

Weight: The average weight of the home patients was unaltered at two years, whereas the sanatorium patients, who had gained considerably more weight than the home patients in the first year, lost on the average 5.3 lbs. of which 3.4 lbs. were lost in the first six months of the second year.

ESR: At two years a considerable proportion of both series, namely, 43 (80%) of the home and 40 (62 %) of sanatorium patients still had elevated ESRs : the rate being higher than 20 mm/1 hour. At the end of two years 25% of patients in calcium series compared with 36 % in the isoniazid series had normal ESRs. In the two-year period the fall in the ESR was greater in the cavitated series.

Radiographic Response: The results of the radiographic response in the second year are presented in table IV.

TABLE IV

Radiographic Progress in 2nd year

Series	Patients	(+)	(±)	(—)	R* Change	DTK
Home	57	9%	81%	7%	2%	2%
San	69	12%	80%	3%	6%	0%
Cal	61	8%	80%	7%	5%	0%
INH	65	13%	80%	3%	3%	2%
Cav	42	14%	71%	5%	7%	2%
Non. Cav	84	8%	85%	5%	2%	0%

(+) = Improved
 (±) = Unchanged
 (—) = Deteriorated

R_x change = Treatment changed
 DTH = Death

In the two-year period 9% of 57 home and 12% of 69 sanatorium patients showed radiographic improvement. 80 % of patients receiving isoniazid as well as the same proportion of those receiving placebo showed no radiographic change in the second year. Seven (11 %) of the calcium and four (6%) of the isoniazid series showed radiographic deterioration, treatment being changed in three of the calcium and two of the isoniazid patients. There is a suggestion that the isoniazid series had fared better but the difference are trivial. 71 % in the cavitated and 85 % in the non-cavitated showed no radiographic change in the second year. The great majority of patients without residual cavitation at the end of first year remained without cavitation at the end of second year. Patients who showed residual cavitation at the end of one year fared slightly less well during the second year than did those patients without residual cavitation.

Bacteriological Findings

Table V represents the bacteriological status at 2 years. The patient's disease was classified as quiescent at the end of two years if all the cultures in the last six monthly examinations had been negative. Patients who had more than one positive culture at any time in the second year with no radiographic deterioration, and those who had more than one positive culture at any time in the second year associated with radiographic deterioration, which in every case necessitated a change of treatment, were considered to have relapsed. The relapse rate during the second year in the whole series of patients was 6%.

The bacteriological status at two years was very similar in the three comparisons. Bacteriologically quiescent disease was present in 95% of the home compared with 93% of the sanatorium patients, 93 % of those treated with calcium compared with 94 % of those treated with isoniazid, and 88% of those with cavitation compared with 96% of

TABLE V.

Bact. Status at 2 Years

Series	Patients	Q	R	DTH
Home	57	95%	4%	2%
San	69	93%	7%	0%
Cal	61	93%	7%	0%
INH	65	94%	5%	2%
Cav	42	88%	10%	2%
Non Cav	84	96%	4%	0%
Total	126	94%	6%	1%

Q-Quiescent R=Relapse DTH=Death

those without cavities at the end of the first year. The low percentages of relapses observed in the second year shows the absence of clear-cut benefit of a second year of chemotherapy. Those with the "open-negative syndrome" (i. e., bacteriological quiescence with residual cavitation) did not, however, fare quite well as those without cavitation.

Self-administration of Medicaments

The problem of self-administration of medicaments is always encountered among patients who have to take drugs daily for long periods. The regularity of self-administration of medicine was checked by counting the stock of pills and by the naphtho-quinone-mercuric chloride urine tests (Short and Case 1957; Gangadharam *et al.*, 1958) for isoniazid. Pill counting at surprise home visits revealed incorrect stocks in approximately 20 % of the counts, there being hardly any difference between those who had supervised treatment at sanatorium in the first year and those treated at home. The isoniazid was accepted as readily as the placebo pill. The study of this problem gave the impression that irregularity and inconsistency observed among patients who had to administer the drugs on their own was not attributable to the side of effects, the physical bulk, or to the taste of the pill.

CONCLUSION

1. 117 (93%) of 126 patients had maintained quiescent disease at two years whether they received isoniazid alone or the placebo.
2. Only one death among 126 was recorded. He was a patient from the home series in the first year, having cavitated disease at the end of a year. He received isoniazid in the second year.
3. There was no evidence in this series that a second year of treatment with isoniazid alone conferred any benefit.
4. The persistence of bacteriological quiescence in the second year was not found to be different in the two series of patients whether they had been treated at home or in the sanatorium during the first year.

5. Patients with residual cavitation and negative bacteriology (open-negative syndrome) at one year fared slightly less well in the second year than patients without obvious cavitation.

6. A relapse rate of 6 % was observed among these patients followed in the second year.

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REFERENCES

- GANGADHARAM, P. R. J., MITCHISON, D. A., SUBBAIAH, T. V. & SHORT, E. T., (1958) *Tubercle (Lond.)* 39, 191.
- SHORT, E. T., & CASE, E. M. (1957) *Tubercle (Lond.)* 38, 288.
- Tuberculosis Chemotherapy Centre (1959) *Bull. Wld. Hlth. Org.*, 21, 51.
- Velu *et al*, (1960) *Bull. Wld. Hlth. Org.*, 23, 511.

Influence of Rest, Movement and Work in Cases of Pulmonary Tuberculosis Under Chemotherapy*

By

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(from Medical College, Calcutta.)

Before the advent of modern chemotherapeutic drugs, bed-rest followed by graduated movement was regarded as the back-bone of the treatment of pulmonary tuberculosis. With the introduction of effective chemotherapy, the need for prolonged rest was not deemed essential but the necessity of rest in the initial period is still maintained and advocated. Even before this era one of the author (P.K. Sen) gathered an impression from his studies on Behaviour of Contralateral lung and pleural effusion in ambulatory A.P. treatment and from his association with ambulatory cases that ambulation did not harm the patients appreciably in many instances.

In a communication, published in this Journal he analysed 1075 cases in an effort to determine the influence of rest and movement treated under domiciliary service. His findings seem to show that cases under chemotherapy did have no appreciable influence on the result of treatment whether the patients rested, moved or worked even at the initial period of treatment. This would, naturally, mean that the accepted value of rest is in question and hardship due to enforced rest is not essential. A finding of such nature which goes against accepted views cannot be accepted by one set of studies. The author, therefore, in association with one of his colleagues, planned another study of similar nature and design. The group of cases accepted in this study were, however, under better control.

Material for Study

At the Chest Department, Medical College, Calcutta, out-door treatment is advised for all the registered cases. Home visiting by Tuberculosis Health Visitors are made only for the cases residing in Calcutta. Those among them who are regarded as too ill to attend the outdoor regularly are referred to a special section called "domiciliary section". Besides such cases, other cases for some special reasons are also accepted in this section. Comparatively, bad cases are gravitated to this section. More careful and detailed record of these cases are kept than ordinary outdoor cases and they are often visited by two "domiciliary Medical Officers" at their homes.

This group alone had been accepted for this study. It would, therefore, be realised that this group was regarded to be in need of more rest than average outdoor cases.

Method of Study

On registration to the domiciliary section each patient was advised initial rest and chemotherapy. Drugs (INH & PAS) were supplied free of charge to every patient.

* Paper presented at the XVII All India Tuberculosis and Chest Diseases Workers Conference held at Cuttack in Jan. 1961.

All possible methods for control of chemotherapy at home were adopted. For various circumstances, specially for poverty, rest regimen advised could only be followed by 269 among 2,281 or 18.12% of the patients. After the progress of chemotherapy for some months each patient was interrogated carefully on how they followed rest regimen from the start of treatment. On this information the patients were classified into the following three groups:

W₁, W₂, W₃.

W₁—Those who had generally followed the medical advice of initial rest and there-after graduated movement.

W₂—Those who moved about somewhat against medical advice but did not do usual work.

W₃—Those who continued to do their work not involving manual labour against medical advice.

The result of domiciliary chemotherapy was recorded as: Worse, Stationary, Improved and Quiescent.

Besides this movement, other important factors which might have influenced the result of treatment were supposed to be (a) the duration of treatment, (b) the extent of the lesions as judged, from usual PA view of large-size skiagrams, (c) presence or absence of cavitation as judged from similar skiagrams, and (d) sputum status—positive or negative by smear examination only.

In order to find, as far as possible, the influence of rest, movement and work, the influences of the other main factors had to be assessed in an attempt to eliminate biases.

No case was accepted unless chemotherapy was more than 3 months duration.

Result

In a study of this kind, duration of chemotherapy in different groups should be comparable. Table-I shows the distribution of cases in different groups according to this duration. The duration has been divided into four periods—3-6 months, 6-12 months, 12-18 months and more than 18 months.

TABLE No. 1
Case distribution according to "duration of treatment in rest & movement groups".

Rest & Movement	Duration of chemotherapy in months				Total
	3-6	6-12	12-18	18+	
W ₁ .	95 35.32%	64 23.70%	58 21.56%	52 1.33%	269
W ₂ .	526 29.16%	465 25.72%	435 24.12%	378 20.95%	104
W ₃ .	77 38.69%	50 25.13%	38 19.0%	34 17.0%	199

An analysis of the data shows that there is no great difference in the distribution of cases in the different groups and, therefore, they are comparable. It may be accepted that with shorter period of chemotherapy smaller number will improve or become quiescent. In that light, the group 'W₃' has slight preponderance of shorter chemotherapy cases.

Table-II presents the distribution of cases according to other important factors, namely, the extent of the lesions, presence or absence of cavitation and presence or absence of bacillus in sputum at registration.

The extent of the lesion had been classified into—

Classification of extent of lesions

- I. When the total area involved is not more than the area of one zone roughly.
- II. When the total area involved is more than one, but not more than two zones.
- III. When the total area involved is more than two zones.

TABLE No. 2

Case distribution according to "extent of lesions", "cavitation" and "sputum status" in rest and movement groups.

	Extent of lesions			Sputum Status		Cavity		Total
	I	II	III	Positive	Negative	Present	Absent	
W ₁	66 24.54%	112 41.64%	91 33.83%	135 50.2%	134 49.8%	137 50.9%	132 49.1%	269
W ₂	338 18.74%	784 43.47%	682 37.8%	723 40%	1081 60%	989 54.82%	815 45.18%	1804
W ₃	62 31.15%	53 26.63%	84 42.21%	103 51.76%	96 48.24%	120 60%	79 40%	199

Study of this general table shows that both extent III and cavitory cases somewhat predominate in 'W₃' group.

Consideration of these two general 'over-all' tables seems to show that the group 'W₃' is comparatively slightly worse in having more cases of extent III, sputum positive cases and less duration of chemotherapy.

Table-III presents an over-all picture of the immediate result of treatment in all the groups.

The result of treatment has been classified into—

Worse— Extension of infiltration, and/or enlargement of the cavity and/or new cavitation and/or appearance of new lesion and/or sputum reversion.

Stationary— The lesion and the cavitation and the sputum status remain almost the same.

Improved— Retrogression of infiltration and/or diminution in the size of the cavity and/or sputum conversion.

Quiescent— (a) Lesion must be stable showing adequate fibrosis and retrogression and must not show evidence of cavitation in the ordinary P.A. view of the chest, (b) Three consecutive sputum tests must be negative for AFB, by direct smear examination, (c) No tuberculous toxæmia and exercise tolerance normal.

TABLE No. 3

Table showing the result of chemotherapy in relation to rest & movement without any consideration of other factors.

Working status	Worse	Stationary	Improved	Quiescent	Total
W ₁ (Rest etc.)	35 13%	47 17.47%	136 50.55%	51 18.95%	269
W ₂ (Casual)	161 9%	293 16.24%	1059 58.7%	291 16.13%	1804
W ₃ (Light)	24 12%	56 28%	84 47%	35 17.59%	199

Counting “improved and quiescent” cases together as indicative of good result, it will be seen from the above table that this result was for ‘W₁ 69.50%, ‘W₂’: 74.83% and ‘W₃’: 64.59%.

Study of distribution of cases had shown before that the groups ‘W₁ and ‘W₂’ are about equal whereas ‘W₃’ was somewhat worse. Best result, however, has been obtained for group ‘W₂’. This seems to show that moderate movement did not harm and, possibly, even normal work not involving heavy manual labour also did not harm.

In order to scrutinise the biases, the results of treatment were checked further. As duration of treatment may have the greatest influence on the result of treatment, the cases in different ‘rest and movement’ groups were compared under similar durations of chemotherapy and in relation to other important factors, namely, extent of lesions, cavitations and sputum status. For such a purpose the duration of treatment has been divided into “upto 12 months” and “more than 12 months” and “improved” and “quiescent” cases were classed together and shown as “improved” in the result of treatment.

The findings are presented in tabular form.

TABLE No. 4

Result of treatment (improvement) in relation to extent of lesions and duration of treatment in different groups.

Extent	I		II		III	
	-12	12+	-12	12+	-12	12+
Total : W ₁	31	35	63	49	60	31
Improved :	31	32	42	40	20	12
Percentage :	100%	91.43%	66.66%	81.63%	33.33%	38.73%
Total : W ₂	179	159	408	376	404	278
Improved :	166	128	336	283	269	168
Percentage :	93.3%	80.50%	82.35%	75.26%	66.58%	60.43%
Total : W ₃	33	29	33	20	61	23
Improved :	29	22	22	14	25	7
Percentage :	87.87%	75.86	66.66%	70%	40.98%	30.43%

The figures show that the more the extent of the lesions the worse was the result in each chemotherapy period and in every group.

It would also be seen that group 'W₉' had generally done better than 'W₁' and 'W₃' in almost all categories of extent of the lesions. It is also noteworthy that in cases with "extent III—lesions" 'W₃' did not fare worse than 'W/' group. Only in milder forms of the disease, that is extent I, 'W₃' group did somewhat better than the others.

From these findings it may be justified to conclude that work and movement did not affect appreciably the result of chemotherapy in cases with different extent of the lesions.

Cavitation

TABLE No. 5

Result of treatment (improvement) in relation to presence and absence of cavitation and duration of treatment in different groups.

CAVITY		PRESENT		ABSENT	
		-12m	12+	-12m	12+
W ₁	Total	74	63	80	52
	Improved	34	36	68	48
	Percentage	46%	57%	85%	92%
W ₂	Total	566	423	425	389
	Improved	379	250	392	329
	Percentage	67%	59%	92%	84%
W ₃	Total	78	41	49	30
	Improved	32	19	45	24
	Percentage	41%	46%	92%	80%

It will be seen that the result in non-cavitory cases were far better than the cavitory cases. In the non-cavitory group work and movement do not seem to have affected the result appreciably. In the cavitory cases, however, 'W₃' group fared worse than the others and W₂ group better than the others.

It may, therefore, be true that in cavitory cases normal work should not be permitted at the initial period but moderate movement does no harm.

Sputum Status

TABLE No. 6

Result of treatment (improvement) in relation to sputum status and duration of treatment in different groups.

SPUTUM STATUS		1 POSITIVE		NEGATIVE	
		-12m	12m+	-12m	12m+
W ₁	Total	79	57	71	58
	Improved	39	38	64	46
	Percentage	49%	67%	90%	79%
W ₂	Total	408	315	583	498
	Improved	275	202	496	377
	Percentage	67%	64%	85%	76%
W ₃	Total	65	38	62	34
	Improved	32	22	44	21
	Percentage	49%	58%	71%	62%

The figures show that sputum negative cases had better results than the sputum positive cases in all chemotherapy periods and in all groups.

The table also shows no appreciable difference between W_1 and W_2 groups except for '—12' month chemotherapy group where W_2 fared better. As a whole W_3 group had somewhat inferior result both in sputum positive and negative cases and in all chemotherapy periods.

It may, therefore, be concluded that moderate movement did no harm but full-time work, even of a lighter nature, affected the result somewhat injuriously.

The merit of an investigation of this nature depends largely on the accuracy of the data and assessment of the influence of one factor by elimination of all other possible influences that may cause a bias. For accuracy of data as much care as possible was taken. The course and the result of treatment in tuberculosis are affected by a host of factors—some are known and many others are still unknown. All such influences cannot be neutralised. There had been, therefore, limitations for this study in this regard. We do not know whether such a limitation could ever be avoided. But, it is certainly possible to scrutinise the data in greater detail and also to make controlled studies. The authors, therefore, look forward for such studies by their esteemed colleagues in other places also, as if it is proved beyond doubt that work does not harm then it will be an important advance in knowledge.

From this study, the authors feel justified to broadly conclude that moderate movement, even at the initial phase of treatment, cause no harm to patient even in an advanced stage of the disease. Full time work, not involving heavy manual labour may have some injurious effect specially in cases with extensive disease with cavitations and positive sputum. We are, however, not quite definite about it as the inferior result may well be due to accumulation of bad cases in this group.

This study, therefore, broadly supports the findings of a former study by P. K. Sen.

SUMMARY

1. An attempt has been made to determine the influence of rest, movement and work in cases under domiciliary chemotherapy.
2. Two thousand two hundred seventy-two cases of a special unit of the chest department, Medical College Hospitals, Calcutta, were investigated. No case was accepted who had less than 3 months chemotherapy.
3. The cases were classified into 3 groups according to rest and movement from the start of treatment: ' W_1 ' (rested), ' W_2 ' (moved and worked moderately), ' W_3 ' (did full time work not involving heavy manual labour).
4. The groups were generally comparable in social, environmental and financial status.
5. Comparative study of the groups with regard to duration of chemotherapy (INH & PAS), extent of the lesions, cavitory lesions and sputum status showed that ' W_3 ' group is somewhat worse in all these regards.
6. Comparative study of the result of treatment showed that the ' W_2 ' group fared as well as ' W_1 ' or even slightly better whereas ' W_3 ' was slightly worse. The latter may well be due to accumulation of more serious cases in this group.
7. In view of these findings it may be accepted that work and movement, even at the initial stage of the treatment, is not harmful for an average case. But for more serious cases full time work may not be quite safe.

ACKNOWLEDGMENT

The authors are grateful to the staff of the 'domiciliary unit' of the Chest Department, Medical College, Calcutta.

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REFERENCES

P. K. SEN:

1. Domiciliary Treatment of Pulmonary Tuberculosis: The Indian Journal of the Tuberculosis: Vol. II., No. 3, June, 1960.
2. Behaviour of Contralateral being in ambulatory cases under unilateral Pneumothorax treatment, Indian Medical Gazette, Vol. 77, No. 10, Oct. 1942.
3. Pleural effusion in Artificial Pneumothorax, its incidence in cases treated from the beginning in an Outpatients, Deptt., Indian Medical Gazette, Vol. 78, No. 10, Oct. 1943.

A Concurrent Comparison of Four Regimens of Chemotherapy in the Domiciliary Treatment of Pulmonary Tuberculosis in South India*

By

C. V. RAMAKRISHNAN AND S. VELU

(from Tuberculosis Chemotherapy Centre, Chetput, Madras-31)

A number of problems concerning the chemotherapy of tuberculosis had to be solved before considering a mass campaign for the control and eradication of the disease in a population. The first and the most important need was an investigation of the efficacy of treatment at home as compared with treatment in the sanatorium including a study of the risks to which contacts of patients at home might be exposed. These questions were answered in the result of studies, which have already been reported from the Tuberculosis Chemotherapy Centre, Madras (Tuberculosis Chemotherapy Centre 1959, 1960). The place of isoniazid which is a cheap, easily acceptable drug in the domiciliary treatment of pulmonary tuberculosis had to be determined. Another study which forms the basis of the present paper was carried out to determine the relative merits of 3 different regimens of isoniazid alone compared with a standard form of oral chemotherapy comprising isoniazid and PAS which had previously been shown to be effective in the domiciliary treatment of poor patients in Madras City. All the patients who were investigated in this study reported with symptoms at the local chest clinics and mass miniature radiography was not employed as a source of cases.

The Treatment Regimens

Table 1 describes in detail the different treatment regimens that were followed in this study. Four treatment regimens were studied; the duration of treatment being a period of 12 months. One, designated PH, was a combination of isoniazid and PAS given in 2 equal divided doses. From an earlier study at this Centre, this combination had already been proved to be a very effective form of chemotherapy when given to

A Concurrent Comparison of 4 Regimens of Chemotherapy in the Domiciliary Treatment of Pulmonary Tuberculosis in South India

I. Dosage of Drugs for 100 lb. Patient

Chemotherapy	Isoniazid	PAS	Patients
PH— 2 doses	200 mgm 4.6 rag/kg	10 g 0.23 g/kg	90
HI-1— 1 dose	400 mgm 8.7 mg/kg	—	70
HI-2— 2 doses	400 mgm 8.7 mg/kg	—	68
H— 2 doses	200 mgm 4.6 mg/kg	—	87

* Paper presented by C.V. Ramakrishnan at the XVII All India Tuberculosis & Chest Diseases Workers' Conference held at Cuttack in January 1961.

tuberculous patients in the Madras community on a domiciliary basis. The other three regimens designated HI-1, HI-2 and H consisted of isoniazid alone. Of these, the H series received the same low dosage of isoniazid in the same rhythm as that contained in the PH series. The other two regimens, namely HI-1 and HI-2, contained the largest dose of isoniazid which was considered likely to prove non toxic. Of these, the HI-1 was given in one dose and HI-2 in two equally divided doses. A daily dose of 200 mg of isoniazid with a mean daily dosage of 4.6 mg/kg body weight was used in the PH and H series. The HI-1 and HI-2 series received 400 mg of isoniazid with a mean daily dosage of 8.7 mg/kg body weight. The dose of PAS (Sodium salt) was 10 g per day in the PH series and the mean daily dosage was 0.23 g per kg body weight.

The allocation of the different treatment regimens was undertaken by the statistical department of the Centre by following the principle of random sampling numbers. Prior to allocation neither the clinicians nor the statisticians were aware of the chemotherapy which any individual patient would receive. At the end of the intake, there were 90, 70, 68 and 87 patients in the PH, HI-1, HI-2 and H treatment series respectively.

General Management

The pre-treatment investigations on these patients consisted of a record of the weight, a clinical examination, an ESR estimation and an X-ray of the chest. In addition, four specimens of sputa (2 'spot' specimens produced within a matter of few minutes at the Centre and 2 'collection' specimens which were collected overnight in the home), were examined for tubercle bacilli by smear and culture. Tests of sensitivity to isoniazid and PAS on two cultures were performed as a routine. A detailed enquiry into previous chemotherapy was also made. Patients attended the clinic once a week for the supply of drugs and the Health Visitors made weekly visits to patients' homes in the earlier months (less frequent home visits were made by the social workers and doctors). A minimum of two home visits during the later months, one to deliver a sputum bottle and the other a surprise one to count the stock of pills and collect specimens of urine were always performed by the Health Visitor. The assessment of progress was made at monthly intervals when an X-ray of the chest and the examination of two sputum specimens was undertaken by smear and culture. From the third month onwards, a pair of laryngeal swabs was also examined by culture. The regularity of drug taking by the patients was checked by means of pill counts and by testing the urine for PAS (Simpson 1956) and isoniazid (Short & Case, 1957; Gangadharam *et al.*, 1958). These patients were advised to rest at home as much as possible, but many were ambulant during the whole period of treatment and several returned to work before the doctor had certified them fit.

Pre-treatment Status of Disease

Most of the patients were between the ages of 25 to 44, all were ill, showed bilateral advanced cavitated lesions on their chest X-rays and had bacteriologically proven pulmonary tuberculosis. More than 90% of patients had cavitated disease, 65 to 70% had far advanced disease, about 80% had 3 or more lung zones involved. Sputum cultures from all the patients were positive for tubercle bacilli, the organisms being sensitive to isoniazid. At least 80% of them had smear positive results at the first examination. In any controlled clinical trial, it is important that the pre-treatment condition of the patients should be similar in the groups compared. The pre-treatment condition of the patients in each of the four different treatment series was very similar in respect of general condition, weight and ESR (not tabulated). The similarity in the radiological and bacteriological findings in the various treatment groups is shown in table II.

II. Status of Disease on Admission

	PH	HI-1	HI-2	H
Cavitated	91%	99%	93%	91%
Far advanced	73%	66%	65%	70%
3 or more lung zones	82%	81%	78%	80%
Positive on smear	78%	83%	83%	84%
Total patients	90	70	68	87

Results of Progress during the year

There was practically no difference in the weight and ESR changes between the series of treatments at the end of one year. Table III gives the percentages of patients in the four different series, classified on the basis of radiographic changes observed during the year. There were 5 tuberculous deaths during the 12-month period, the numbers being one in the PH, one in the HI-1 and 3 in the H series. 33 patients had their chemotherapy changed because of radiographic deterioration confirmed by the independent assessor, Dr. K. S. Sanjeevi, who was not aware of the treatment regimen which any individual patient was receiving. 2 other cases had change of treatment, one because of a serious clinical deterioration and one because of a profuse haemoptysis. 7 patients had to have their treatment changed because of toxicity to either isoniazid or PAS. One PH patient developed a hypersensitive reaction to PAS and could not be desensitized. 5 HI-1 patients and one HI-2 patient developed peripheral neuritis necessitating change of treatment.

III. Radiographic Changes during the Year

	PH	HI-1	HI-2	H
Improvement	94%	86%	76%	71%
No Change, and Deterioration	3%	6%	2%	8%
Treatment Changed	1%	8%	21%	17%
TB Death	1%	8%	2%	3%
Total patients	86	64	66	86

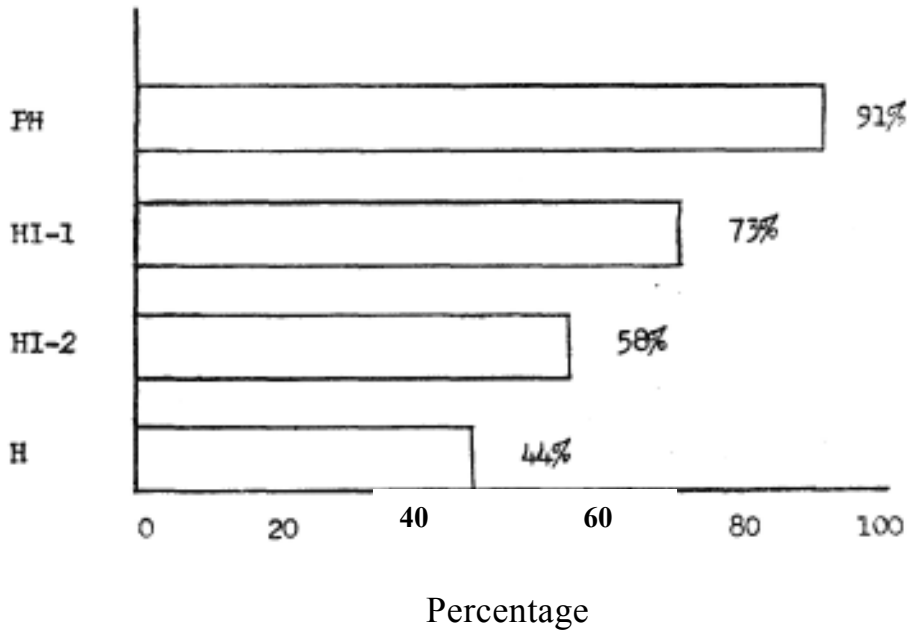
Radiographic Change

At the end of the year 94 % of patients on combined chemotherapy showed definite radiographic improvement, 86% showed similar improvement in the HI-1 series, 76% in the HI-2 series and 71 % in the H series. These figures indicate that the combination of PAS and isoniazid was the most effective form of chemotherapy, with the HI-1 treatment the next most effective while the HI-2 and H regimens of treatment were found to be relatively unsatisfactory.

Bacteriological Changes

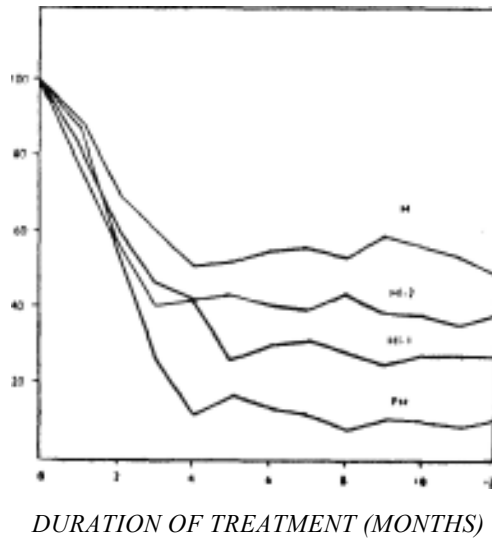
The result of the bacteriological response to treatment is shown on the bar charts presented as Figure I. The intensity of bacteriological investigation was high as an average of 38 cultures were examined for each patient during the 12 months. The

Fig. 1. Patient with Quiescent Disease at the end of 12-Months



disease was regarded as quiescent if all cultures taken during the last 3 months of treatment (average 9) were negative; if two or more positive cultures were found during this period the disease was considered to be active. Figure 2 shows that whilst by the end

Fig. II. Percentage of Patients each month with atleast one Positive Culture Result from Multiple Bacteriological Specimens (Sputum and Laryngeal Swabs)



of the fourth month 90% of the PH series had converted only 60 to 70% of the HI-1 series, 60% of the HI-2 series and about 50% of the H series had shown conversion. From the fourth month until the end of the year the position remained almost stationary. At the end of 12 months the majority of PH patients attained bacteriological quiescence

(Table IV), and the percentage of active cases in each treatment group ranged from 7 to 35 per cent.

IV. Status at 12 Months

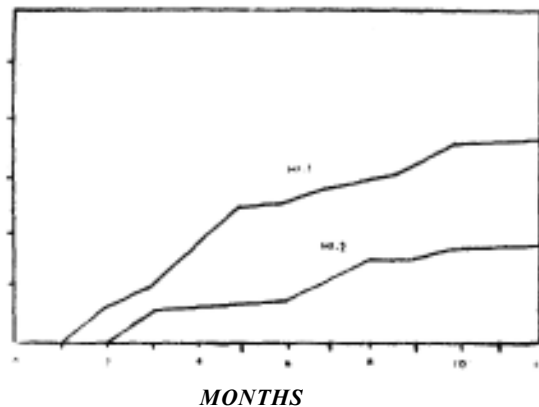
	PH	HI-1	HI-2	H
Quiescent	91%	73%	58%	44%
Active	7%	19%	20%	35%
Deteriorated	1%	8%	21%	17%
TB Death	1%	0%	1%	3%
Total patients	86	64	66	86

Resistance to isoniazid emerged rapidly in the three isoniazid alone series and more slowly in the PH series. From six months onwards nearly all the positive cultures in all four series were isoniazid-resistant.

Toxicity

Three cases of toxicity due to PAS, were encountered in the PH series; desensitisation to the drug was possible in 2 cases but treatment had to be changed in the third. Toxicity to isoniazid in the form of peripheral neuritis developed in 20 cases. This occurred in one of the PH series, 13 of the HI-1 series and 6 of the HI-2 series. None of the patients in the H series developed this complication. The first symptoms of peripheral neuritis, which were mainly sensory, occurred between the 2nd to the 10th month of treatment (Fig. 3). The condition developed very early in the HI-1 series and rather slowly in the HI-2 series. All the patients who developed this complication were found to have high mean serum isoniazid levels. Mental disturbance occurred in one of the cases of peripheral neuritis who had received the high isoniazid regime in a single dose. His symptoms were of extreme apprehension, and of impending death, but within three months of change of treatment his mental state had returned to normal.

Fig. III. Cumulative Percentages of Patients in the HI-1 and HI-2 Series who developed Peripheral Neuritis During 12 Months



Conclusion

The combination of isoniazid plus PAS has been found to be a most satisfactory and effective form of treatment for pulmonary tuberculosis in the domiciliary manage-

ment of patients drawn from the poor urban community of Madras city. Treatments consisting of isoniazid alone given daily in two equally divided doses, whether it was 400 mg or 200 mg per day, have not proved to be very satisfactory forms of chemotherapy. The high dose of isoniazid (7.8 to 9.6 mg/kg) given as a single dose was more effective than the other two isoniazid alone regimens but it was associated with a high incidence of toxic complication in the shape of peripheral neuritis.

ACKNOWLEDGMENTS

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REFERENCES

- GANGADHARAM, P.R.J., MITCHISON, D.A.; SUBBAIAH, T.V. & SHORT, E.T., (1958) *Tubercle (Land.)* 39, 191.
- SHORT, E.I. & CASE, E.M. (1957) *Tubercle (Land.)*, 38, 288. Tuberculosis Chemotherapy Centre (1959) *Bull. Wld Hlth Org.*, 21, 51. Tuberculosis Chemotherapy Centre (1960) *Bull. Wld. Hlth. Org.*, 23, 535.

News & Notes

Tuberculosis Workers to Meet in Bangalore

The next conference of Tuberculosis and Chest Diseases workers in India will be held in Bangalore early in 1962. This will be eighteenth conference organised by the Tuberculosis Association of India. Dr. R. N. Tandon, formerly Professor of Tuberculosis, King George Medical College, Lucknow is the President of the Conference.

Main subjects selected for presentation at this conference are : Changes in the TB prevalence following a TB control programme over seven years in a South Indian Rural Community; (2) Limitations of single film diagnosis in Mass X-ray Surveys; (3) Problems of self administration of drugs in domiciliary treatment; (4) Post vaccination allergy after BCG vaccination; and (5) disease among household contacts of tuberculous patients at the first and subsequent examination. There will be panel discussions on "Tuberculosis Control" and "Pulmonary Carcinoma" at the conference.

It is expected that a prominent TB expert either from USA or UK may attend this conference to present a paper on the latest position of treatment of tuberculosis with special reference to chemotherapy.

Workers in the tuberculosis field may contact the Secretary, Tuberculosis Association of India, 3, Red Cross Road, New Delhi-1, immediately, if they wish to present papers at the conference.

New Seal Design

Design for the TB Seal for the 12th Seal Campaign organised by the Tuberculosis Association of India has now been selected. Out of a large number of designs sent in for the Seals by a number of artists from different parts of India, the one submitted by Mrs. Mehroo J. Wadia, a Delhi artist was selected. The design depicts 'an age-old Indian Folk dance with the dancer on horse-back, the theme of which symbolises vitality and energy'.

1962 Tuberculosis Health Visitors' Course

The Tuberculosis Health Visitors' Course organised by the Tuberculosis Association of India will be held from January next. The duration of the course is one year of which one month will be in the College of Nursing, seven months in the New Delhi TB Centre and one month in the Lady Linlithgow Sanatorium, Kasauli. The candidates will be examined at the end of nine months training and those who are successful will be required to do practical work in home visiting for three months at the New Delhi TB Centre. Certificates will be awarded at the end of one year after satisfactory completion of practical training in the field. The minimum qualification for admission to this course is Intermediate with Science/or Hygiene and Physiology in the matriculation.

Applications for this will be received sometime in October this year. A press note in this regard will be issued in October, 1961.

XVIth International TB Conference, Toronto

The Sixteenth International TB Conference will be held in Toronto, Canada, from 10th to 14th September, 1961. Dr. G. J. Wherret of Canada will be its President.

Dr. P. V. Benjamin, Technical Adviser to the Tuberculosis Association of India, has been selected Chairman of the Panel discussion on "Methods of improving and checking the taking of the prescribed drugs by tuberculous patients" (Study of the problem in consideration of the different sociological and economic conditions prevailing).

IUAT Membership

The Tuberculosis Association of India recommends to the International Union Against Tuberculosis, Paris, names of those who wish to become ordinary members of that Union from India for the year 1961. Membership fee is Rs. 21/- per year. Members of the Union will receive, free of cost, copies of the quarterly bulletin and newsletter published by the Union. Those wishing to enrol themselves as Ordinary Members may write to the Secretary, Tuberculosis Association of India, 3, Red Cross Road, New Delhi-1.

Dr. S. N. Bansali Charitable Trust Prize

The Bombay Obstetric and Gynaecological Society has invited two essays on "Any original work on human sterility" for the award of Dr. S. N. Bansali Charitable Trust Prize for the year 1960 and "Pathology and management of Uterine Prolapse" for the award of Dr. Herculano De Sa Silver Jubilee Prize for the year 1961. The value of both the prizes are Rs. 500/- and Rs. 250/- respectively.

The competitions are open to Registered Medical Graduates of any statutory Indian University and Registered Medical Licentiates of Examining Bodies in India.

For full details and rules governing the award of the prizes please write to the Honorary Secretaries, Bombay Obstetric and Gynaecological Society, Purandare Griha, Chowpatty Sea Face, Bombay-7.

Health Visitors' Course, Madhya Pradesh

Tuberculosis Health Visitors' Course was organised in the M. R. TB Hospital, TB Clinic, Malhargunj and the M. G. M. Medical College, Indore, under the auspices of the Director of Health Services, Madhya Pradesh. The course was conducted strictly in accordance with the Syllabus and requirements prescribed by the Tuberculosis Association of India.

Candidates who wish to undergo this training and the States who may wish to depute candidates to this course may contact Director of Health Services, Madhya Pradesh, Indore.

The Indian Journal of Tuberculosis

ABSTRACTS

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Abst. No. 3

Diagnosis of Tuberculous Meningitis

Better social conditions, intensive public health measures, prophylactic treatment of primary tuberculous infection with antituberculous drugs and B.C.G. inoculation to the new born are the various factors to reduce the incidence of tuberculous meningitis. In spite of all these factors cases of this disease continue to be admitted in our hospital and the effective and powerful drugs fail to act because of delay in diagnosis.

Early diagnosis is very important because effective treatment is available with streptomycin, Isoniazid, p-amino-salicylic-acid and steroids.

Patients treated late in the disease still often die and the survivors often left with good neurological damage.

Patients have been classified into three groups in early, medium and advanced stages.

The common features of early stage are fever, vomiting and apathy. Tuberculous meningitis should be suspected when no other adequate cause can be found especially if irritability is combined with periods of drowsiness, constipation is invariable. Sign of meningeal irritation may be absent.

Early diagnosis depends upon doctor's suspicion being aroused.

A history of contact with known case of tuberculosis is of great significance.

A recent history of measles and meningitis is regarded as suggestive.

In suspicious cases a tuberculin test should be done.

A negative result is rare in early stage of the disease where as a positive test is highly significant.

Ophthalmoscopy may show choroidal tubercles especially when there is associated miliary tuberculosis. A chest radiograph may show a primary complex or the snowstorm appearance of miliary tuberculosis, but a normal film does not preclude diagnosis.

Lincoln and her co-workers stress that signs of mild upper respiratory infection are not rare and do not negative the diagnosis especially when fever, lethargy and irritability seems out of proportion in their severity.

In the middle stage of the disease specific neurological signs make their appearance. Nuchal-rigidity is common. A positive kernig rare. Cranial nerve palsies spasticity and blurring of consciousness thoroughly investigated. The urgency is more under the age of 3 years because progression of disease is rapid in that age group. The child is semi-comatose. Head retraction and + kernig sign are common and so also decerebrate rigidity.

A crack pot sound on percussion of skull and frank papilloedema are other signs.

Patients recovering from advanced stage of disease show permanent neurological sequelae such as hydrocephalus, blindness, deafness, spastic palsies and mental deficiency.

Confirmation of diagnosis is obtained by examination of cerebrospinal fluid. The C.S.F. will be clear or slightly opalescent. Cell count is raised to 50—500 c m.m. and Lymphocytes predominate over polymorphonuclear leucocytes. These findings can exclude pyogenic meningitis, but similar results are seen in virus infections, but history in virus infections is more sudden. History of contact, a positive skin test, positive chest radiograph or choroid tubercle are in favour of a tuberculous etiology.

In tuberculous meningitis the sugar content of C.S.F. is reduced below 50mg. per 100 ml. in about 90% a finding which excludes viral infection. The protein content is higher above 50 mgm. per 100 ml.

The chloride content falls too late in disease to be of diagnostic importance.

Acid fast bacilli may be demonstrated in centrifuged deposit or the pellicle. Culture is not helpful in early diagnosis.

(Leading Article, B.M.J. 1306, May 6, 1961).

Digitalis in Surgery Extension of Classical Indications

20-30 per cent patient over the age of 60 have cardiac complication after intrathoracic resections. 29 per cent of the complications are after pneumonectomy.

Atrial fibrillation and/or atrial flutter are the commonest complications and these respond to digitalis.

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Pulmonary emphysema and/or dyspnea on exertion are the two most important factors in the preoperative evaluation of patients facing thoracic surgery.

Routine Digitalization is recommended for all patients over 60 years of age.

(Myson W. Wheat and Thomas H. Burford. *Jour. Thor. Cardiovascular Surgery* Vol. 41, No. 2 Feb. 61).

Needle Biopsy of the parietal pleura in Tuberculous Effusions

In 69 patients of pleurisy with effusion biopsy was done from one to three times.

Of the 69 cases, 45 had no pulmonary tuberculosis and 24 were with pulmonary tuberculosis.

Tuberculous etiology was established with biopsy in 66 per cent, whereas pleural fluid culture were positive in 23-48 per cent.

Tuberculosis was established as the etiology in all but eleven cases both histologically and bacteriologically.

Needle biopsy is a single most important diagnostic procedure. It is simple, safe and repeatable.

(William Weiss Di-chest, Vol. xxxix, No. 3, March, 1961).

Cycloserine Treatment of Out-Patients with chronic drug resistant pulmonary tuberculosis

Twenty-four patients with chronic drug resistant pulmonary tuberculosis were included in a double blind trial of cycloserine. Of these, 16 patients received cycloserine isoniazid capsule, the rest 8 were in the control group receiving isoniazid alone.

The trial consisted of one month in-patient and eleven months out-patients treatment with a follow up period of six months.

The dosage of cycloserine was 250 mgm. twelve-hourly and isoniazid 150 mgm. twelve-hourly.

Ten patients in the cycloserine group showed weight gain, seven improved clinically and four showed radiographic improvement compared with one patient showing such changes in the control group. Temporary sputum conversion occurred in only three of the cycloserine group patients.

Toxic symptoms occurred in nine out of 16 cycloserine group patients and drug was withdrawn in three. Five out of eight patients in control had toxic symptoms and treatment was discontinued in two.

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[J. Wallace Craig and Howard Williams, *Tub. Land* (1961) 42, 7.]

Control Study of Biologically Active Isoniazid in serum of children with Primary Tuberculosis

Serum Isoniazid concentrations were determined for 770 children to determine the effectiveness of Isoniazid in preventing complications of Primary Tuberculosis.

All were given 8 mgm of Isoniazid per kgm. of body weight and blood specimens were determined two and six hours later. Serum concentrations of biologically active Isoniazid ranged from 0.4 to 6.4 two hours after and 0.2 to 3.2 six hours after.

Serum concentrations for treated children those who had received isoniazid for a year were no different from the values of untreated children those who had received placebo.

There was no association between Isoniazid concentration and changes in tuberculin reaction the appearance of unfavourable pulmonary changes or among untreated children, the occurrence of extra pulmonary complication.

There was no evidence that sex, age, nationality, racial background, extent of roentgenographic involvement or initial tuberculin reaction are related to Isoniazid metabolism.

(Frank W. Mount, Anastasiot A. Anastasides & George A. Schnach. *Am. Rev. Disease*. Vol. 83, No. Feb., 1961.)

Sarcoidosis clinical, Thoracic and Roentgen Features

Of the 45 cases, 20 (44 per cent) had histologic confirmation and in the remainder diagnosis was made after prolonged observation on the basis of clinical, roentgenological and laboratory findings.

Of these 40 (89 per cent) are living cases and all but 3 are working. Of the living cases 60 per cent have been followed for at least five years the longest for 18 years.

5 (11 per cent) died and they survived from 2—9 years. Of these 5 cases, 2 died of chronic corpulmonal and right heart failure, 2 of tuberculosis and 1 of unknown cause.

Roentgenologically regression occurred in 56 per cent, no significant change in 40 per cent and 4 per cent showed progression.

There is no specific treatment but steroids exert a suppressive effect.

(Prognosis is good in majority of patients with sarcoidosis. Samuel Cohan, Mario J. Alluni and David. *Dis. Chest* Vol. xxxix No. 4, April, 1961).