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BHOPAL KILLER GAS (BKG) TRAGEDY

On the fateful night of 23 December, 1984, a large quantity of toxic material contained in Tank 610 of the Union Carbide Factory in Bhopal escaped abruptly in a gaseous form into the atmosphere. This was instantly followed by a human disaster of gigantic proportions in that over 200,000 people inhaled the gas and suddenly took gravely ill. Of these, nearly 2,000 died, mostly within minutes or hours of the exposure, and the remaining over the next few days. The worst affected were those living in close vicinity of the factory in the direction of the prevailing wind. Clinical observations suggest that both the mortality and morbidity in the exposed population were related inversely to the distance between the factory and the habitat of the victims. In other words, higher the concentration, of the gas inhaled, the greater was the severity of the symptoms.

The exact composition of the gas which killed as well as seriously crippled the exposed population being obscure, it will not be inappropriate to refer to this gas as the "Bhopal Killer Gas" (BKG).

The manner in which people died left little doubt that the immediate cause of death was anoxia. There is no way to determine with certainty whether this occurred at the level of lungs i.e. due to failure of exchange of oxygen and carbon dioxide or at the level of the tissues interfering with unloading of oxygen from the oxyhaemoglobin for metabolic needs. It is possible that both mechanisms were involved. Patients with pre-existing lung diseases viz. COPD, bronchial asthma, pulmonary tuberculosis undoubtedly were more seriously affected than those with relatively healthy lungs.

The survivors suffered from a variety of symptoms indicating multi-system involvement, chiefly respiratory, ophthalmic, gastrointestinal, neuropsychiatric and musculoskeletal. These patients were treated in the hospitals, in special camps as out-patients and in their homes. The mainstays of the treatment were life supporting measures like maintenance of fluid electrolytes, acid base balance, oxygen inhalation, bronchodilators, antibiotics and corticosteroid drugs. The entire medical and para-medical personnel of Bhopal, especially the staff and students of the Gandhi Medical College deserve the highest compliments for managing these patients in overwhelming numbers so efficiently and effectively, in spite of meagre resources and lack of authentic and precise scientific information. But for their tireless efforts, excellent team work and dedication, many more lives would have been lost or crippled,

Even today, nearly a year after the BKG tragedy, thousands of victims continue to suffer from a chronic form of illness with clinical manifestations more or less on the pattern of the acute phase of the disease. The major

symptoms comprise breathlessness, cough, expectoration, chest pain, inability to work, bodyaches, loss of memory, lack of concentration, epigastric pain, restlessness, giddiness loss of appetite and visual defects. Detailed investigations of these patients are in progress. Preliminary observations upto October, 1985 have been summarised elsewhere in this issue.

The two most important aspects of the BKG Tragedy are ; (i) the disease complex which followed inhalation of the toxic gas is entirely new to the medical science; (ii) the toxic gas was an extremely reactive substance and the possibility of developing hitherto unsuspected complications/sequelae in the exposed population in the future cannot be overlooked. Thus, the overtly diseased as well as the apparently healthy among the exposed population of Bhopal will need to be kept under surveillance for a long time to come—may be several decades—and some of them, perhaps, for life.

— *S. K. Jain*

THE SIGNIFICANCE OF DRY COUGH, BREATHLESSNESS AND MUSCLE WEAKNESS*

A.S. PAINTAL**

Introduction

I am grateful both to the Tuberculosis Association of India and the Ranbaxy Laboratories Limited for the privilege of delivering the Hanbaxy—Robert Koch Oration of 1985. It is appropriate that I should be delivering it at Shillong for although this delightful city cannot be regarded as being at high altitude, it is nevertheless located near the Himalayas which are partly the source of the information on which the present talk, is based. Indeed, after the aircraft in which I came, left Patna for Bagdogra one could see on the left the great majesty of the Himalayas and the Kunchenjunga and how significant dry cough, breathlessness and muscle weakness must be in high altitude regions where man has some habitations. However, these associations were not the reasons for the choice of the title of my lecture. The reasons were different.

Choice of title: It was on the 1st of May 1985 that I was asked by the Secretary General of the Tuberculosis Association of India to give him the title of my lecture. At that time we were involved in the aftermath of the Bhopal gas tragedy (particularly, Prof. S.K. Jain who will be speaking after me) and were trying to evaluate the extent of pulmonary damage suffered by the people who had inhaled highly toxic doses of methyl isocyanate gas (MIC) but had managed to survive. We were apparently made responsible for this aspect of the investigation as implied in the Report of the Indian Council of Medical Research, dated December 33, 1984 entitled "The Bhopal Disaster—current status (the first nine days) and programme of research". However, as is known, parallel studies were also conducted. These were, to a considerable extent, based on the mistaken notion of a German toxicologist, Max Daunderer of Munich that cyanide or a chemical impersonator was present in the mixture that escaped from the MIC tank. And so, Max Daunderer began the treatment of the victims with sodium thiosulphate and although this treatment was immediately stopped and Daunderer was sent home (Lepkowski, 1985) the treatment was continued by others, along with respiratory and other

controlled studies, the IC MR put an end to the controversy four days ago as reported in the Statesman of Nov. 12, 1985.

One of the important reasons for the interest in the Bhopal gas tragedy arose from the fact that the victims died of pulmonary oedema. Those who survived pulmonary oedema complained of severe muscle weakness in addition to cough and breathlessness. In several cases, severe muscle weakness was the major complaint—they were unable to carry out tasks involving physical exertion and the children could run only a little, if at all. To me, it was clear that since MIC gas produced pulmonary oedema (of which the victims died) it followed that there would be an intense barrage of impulses from the J receptors which would cause inhibition of somatic muscles through the J reflex (Paintal, 1970) and this would manifest itself as muscle weakness (Paintal 1985; 1986). This conclusion, which was supported by the fact that no evidence for any neurological lesions had been found, was broadcast by the British Broadcasting Corporation on Dec. 12, 1984. Subsequent events have supported what had been predicted since the patients recovered from muscle weakness to a considerable extent after interstitial oedema got less (leading to reduction in the activity in the J receptors) along with reduction of dry cough and breathlessness. This accounts for the title of my lecture.

Respiratory Symptoms

The chief complaints of patients with chest diseases are cough and breathlessness. Some also complain of pain in the chest and there are a few who, if questioned further, complain of muscle weakness but neither the physician nor the patient think that this is of significance as far as his respiratory problem is concerned.

Breathlessness: There are several mechanisms that are responsible for the sensations of breathlessness. Some of these, particularly those associated with obstruction in the airways, are apparently located in the chest wall and diaphragm (see Campbell and Guz, 1981; Killian and Campbell, 1985). Good evidence

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supporting this view is provided by the observations of Campbell et al (1969) showing that neuromuscular blockage by curare reduces or abolishes the severe distress and the intractable urge to breathe during breath-holding; this indicates that some feedback from the respiratory muscles is necessary (Killian and Campbell, 1985). However, it must be realized that although the contribution of sensory information from the respiratory muscles may be important in the generation of sensations of distress, the respiratory drive to breathe arising from the lungs plays the more dominant and primary role in the generation of the sensation of breathlessness. Which are the receptors responsible for this sensation?

At present, one can say (that there are three main groups of sensory receptors in the lungs and airways (Paintal, 1983c) i.e. the pulmonary stretch receptors (both slowly and rapidly adapting), the C-fibre bronchial receptors of the 'Cole-ridges' and the type J receptors. Earlier (see Paintal, 1973; Widdicombe, 1974) and also presently (e.g. see Irzebski, 1983; Sant' Ambrogio and Remmers, 1985) the rapidly adapting receptors (also called 'irritant receptors' at one time) were regarded as being a separate group of receptors which were involved in the excitation of breathing and also in the production of breathlessness. However, as pointed out (Paintal, 1977a), stimulation of these receptors by frequent and forceful respiratory movements which would inevitably lead to intense stimulation of these receptors does not produce any unpleasant sensations. On the other hand since many of their properties are similar to those of the slowly adapting pulmonary stretch receptors, it seems likely that they might produce sensations or relief of breathlessness because such relief is produced by the stimulation of pulmonary stretch receptors, as shown by Fowler (1954) and Mithoefer (1959).

It is possible that the C-fibre bronchial receptors may be associated with sensations of breathlessness but so far one is not in a position to say to what extent they are involved, particularly because it now appears that stimulation of these receptors in cats and dogs does not produce the respiratory reflex effects (Anand et al, 1985) that had been attributed to them earlier (Coleridge et al, 1983). Thus, the only receptors that can almost certainly be implicated in the genesis of breathlessness are the type J receptors which are stimulated in all conditions leading to increase in interstitial oedema at the alveolar level (see Paintal, 1983 c) i.e. conditions that produce dyspnoea in man. It should be noted that these receptors must be stimulated during exercise that leads to increase in pulmonary blood flow (corresponding

to increase in cardiac output). This is indicated by the fact that doubling blood flow increases their activity to a level that produces marked reflex effects (Anand and Paintal, 1980). Thus, these receptors must be stimulated during activities involving moderate physical exercise and so it is not surprising that the feeling of breathlessness is such a common normal sensation. In fact, it is the most prominent normal visceral sensation whose importance has so far not been fully appreciated (Paintal, 1986a; 1986b). Everyone has experienced the sensation of breathlessness but the vast majority do not complain of it as they expect to experience it during physical exercise. Thus, it is ignored. It is when one experiences the sensation at a level of physical exertion that normally did not produce breathlessness earlier that one takes notice and complains of it to the physician who then labels it as dyspnoea. However, it is not about this that I wish to speak about mainly, today, but about cough.

Origin of cough: Most physicians assume that all coughs are due to irritation in the throat (arising from inflammation etc.) or due to the presence of accumulated secretion in the airways. Some believe that it is due to the stimulation of irritant receptors (i.e. rapidly adapting pulmonary stretch receptors (see Korpas and Tomore, 1979). This view is entirely incorrect as shown by the following argument:

The so-called 'irritant receptors' are stimulated markedly not only by inflation of the lungs but also by deflation of the lungs which *reduces* the discharge of the slowly adapting receptors (Widdicombe, 1954). Thus, by forcefully deflating the lungs from functional residual capacity repeatedly at, say, 120/min one would be producing intense activity in these receptors without increasing the activity of pulmonary stretch receptors much. However, one can demonstrate to oneself that such a manoeuvre does not produce any cough or sensations of irritation in the throat leading to cough and so the possible role of irritant receptors in the genesis of cough is ruled out.

However, cough is certainly produced by receptors in the upper airways as can be shown by the fact that it is so common following mechanical irritants such as bread or biscuit crumbs or inhalation of cigarette smoke by non-smoker. These irritants must be stimulating some hitherto unidentified receptors which are specifically stimulated by mechanical and/or chemical irritants but are *not* stimulated by rapid airflow. It is to be hoped that we will, in the near future, have information about the precise properties and behaviour of these receptors.

A second wrong assumption about cough is that it originates only from the upper airways and pharynx. This arises from the tacit assumption by physicians that cough does not arise following stimulation, of receptors at the alveolar level. This is not correct as we now know that cough can be produced by stimulation of sensory receptors at the alveolar level i.e. the type J receptors, as pointed out by Laszlo (1984) in the textbook entitled "Modern Medicine". Recently, evidence has been obtained to show that cough is produced by natural stimulation of J receptors.

Production of cough in man by J receptors

The knowledge that natural stimulation of J receptors leads to the genesis of cough in man came about by comparing the effects of lobe line with those of high altitude pulmonary oedema (see Paintal 1986a for details). It had been known that intravenous injections of lobeline produced cough and this was used for measuring circulation time. (Lilienfeld and Berliner, 1942). Eckenhoff and Comroe (1951) thought that it stimulated pain endings in the pleura. Subsequently, it was erroneously thought that the effects were due to the stimulation of so-called pulmonary arterial baroreceptors (Stern et al, 1966). However, in 1972, Jain et al reported that lobeline stimulated the J receptors of man because injections of lobeline produced apnoea in man with as short a latency as the apnoea produced by other chemicals e.g. phenyl diguanide and capsaicine in cats, rabbits and dogs which are known to stimulate the J receptors. However, they were reluctant to attribute the cough to the J receptors, apparently because intense stimulation of J receptors of cats and dogs does not produce cough in these animals (see Paintal, 1986a). However, in view of the earlier results of Stern et al (1966) showing that receptors downstream from the left ventricle did not produce cough, the conclusion that cough following injections of lobeline was produced as a result of barrage of impulses in J receptors became inescapable as pointed out in a symposium held in Philadelphia in 1976 (Paintal, 1977 b). At this stage, although one could accept the obvious fact that cough following injections of lobeline was due to the stimulation of J receptors, it was nevertheless possible that this effect was no more than a physiological artefact and that natural stimulation of J receptors in fact did not lead to cough. Therefore, the next question that had to be answered was, does natural stimulation of J receptors produce cough?

The J receptors are stimulated markedly during pulmonary oedema (Paintal, 1969; 1970) and it follows that they must, therefore, be markedly stimulated during high altitude pul-

monary oedema (HAPO) in man. The available information (see Paintal, 1986a) showed that this was indeed the case i.e. dry cough was a prominent feature of HAPO. However, not much attention was paid to this because as already pointed out it was assumed that all coughs were generated following stimulation of sensory endings in the upper airways. Indeed, this was a justifiable assumption as the patients that had been treated for HAPO had, in fact, evidence of infection: in particular, infection of the throat and upper airways had not been, ruled out. The problem about the origin of cough in HAPO was, therefore, reinvestigated and from the data obtained from otherwise healthy young men in whom (here was no evidence of infection of the upper airways, it was found that cough was reported by 96% of the subjects (dry cough by 72%). This cough could, therefore, be attributed in the stimulation of J receptors by HAPO. This conclusion was reported and discussed at the International Congress of Physiology held in Sydney (Paintal, 1983a; 1983b) and has been discussed further subsequently (Paintal, 1986a). In this connection, two important features deserve mention. First, that the dry cough produced by natural stimulation of J receptors is indistinguishable from the common cough produced by irritation of the throat during infections. Second, that the cough produced is not entirely a reflex response but it is, in fact, an effort by man to get rid of the irritation felt in the throat which precedes the cough (Paintal 1983b, Raj, 1984). Thus, it is now easy to see why dry cough is a prominent feature in all pathophysiological conditions in which the J receptors must be stimulated (see Paintal, 1983c). The dry cough so produced would be accompanied by breathlessness, as pointed out above and tachypnoea which is produced by the J receptors (Paintal, 1977a; 1977b; Trzebski, 1983; Coleridge and Coleridge, 1984). The dry cough would also be accompanied by muscle weakness (see below). These two, i.e. breathlessness and muscle weakness would be absent in the case of cough generated by pathophysiological conditions confined to the upper airways.

Muscle weakness—How is it produced! Since it had been shown that the J receptors were stimulated following pulmonary congestion, it was predicted that they would be stimulated during muscular exercise and that they might, therefore, reflexly terminate exercise (Paintal, 1969). This prediction turned out to be true for it was found that stimulation of the J receptors certainly reduced the petellar reflex (Paintal, 1970) (see also Ginzler and Eldred, 1977) and inhibited the monosynaptic reflexes of both extensor and flexor muscles (Deshpande and Devanandan, 1970). This reflex was called the J reflex (Fig. 1).

It was argued, as shown in Fig. 1, that the functional significance of the reflex inhibition of somatic muscles by the J receptors (i.e. the J reflex) was to terminate exercise which in fact

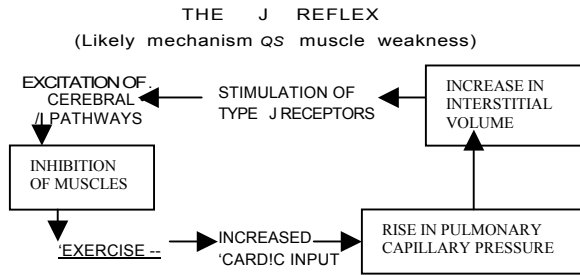


Fig. 1.

Sequence of events in the J reflex showing how exercise is terminated by stimulation of J receptors during exercise. This reflex is also the likely basis for the feeling of muscle weakness in pathophysiological conditions leading to interstitial oedema.

was the only physiological mechanism that led to an increase in their activity under normal conditions. This increase in activity was produced by the increase in pulmonary capillary pressure that must result from the increased cardiac input generated by the muscle pump during exercise. The impulses from J receptors then stimulated certain central pathways that involve the higher centres in the brain which, in turn, provided inhibitory inputs to the motoneurons of somatic muscles and this, by inhibiting muscular contraction, terminated exercise. In the case of man, this inhibition would be manifested as a feeling of muscle weakness because the individual would need to apply more effort in order to overcome the inhibition as first pointed out by Holmes (1922) (see McCloskey, 1982) in the case of patients with unilateral cerebellar lesions.

In conclusion, the symptoms of dry cough, breathlessness and muscle weakness have now acquired special significance in view of the fact that all three can be produced by J receptors and they can, therefore, be used as indices of interstitial oedema. Further, one might be able to use the combination of symptoms in order to differentiate between certain pathophysiological conditions involving the upper airways from pathophysiological conditions at the alveolar level. For example, the dry cough arising exclusively from the throat or the trachea would not be accompanied by obvious breathlessness on exertion and muscle weakness, whereas either or both would feature in conditions involving the alveolar interstitium. Again, in patients with left ventricular or congestive heart failure the appearance of dry cough could serve as a guide to the onset of interstitial oedema.

In such cases, the presence of muscle weakness would be particularly significant especially when there is no evidence for, or reason to suspect, reduction in cardiac output. Thus, it seems that the chest physician would now find it worthwhile to have available reliable non-invasive methods for measuring cardiac output on the one hand and muscle strength on the other.

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REFERENCES

- Anand, A., Dev, N.B. Painlal, A.S. & Ravi, K. Reflex effects elicited after injecting a local anaesthetic into the pericardial sacs of cats and dogs. *J. Physiol.* (1985) 358, 125P.
- Anand, A. & Paintal, A.S. Reflex effects following selective stimulation of J receptors in the cat. *J. Physiol.* (1980) 299, 553-572.
- Campbell, E.J.M., Godfrey, S., Clark, T.J.H., Freedman S., & Norman, J. The effect of muscular paralysis induced by tubocurarine on the duration and sensation of breath-holding during hypercapnia. *CHn. Sc.* (1969). 36, 323-328.
- Campbell, E.J.M. & Guz, A. Breathlessness. In *Regulation of Breathing, Part II*, ed. Hornbein, T.F. (1981) pp. 1181-1195; Marcel Dekker,
- Coleridge, H.M., Coleridge, J.C.G. & Roberts, A.M. Rapid shallow breathing evoked by selective stimulation of airway C fibres in dogs. *J. Physiol.* (1983). 340, 415-433.
- Coleridge, J.C.G. & Coleridge, H.M. Afferent vagal C fibre innervation of the lungs and airways and its functional significance. *Rev. Physiol. Biochem. & Pharmacol.* (1984). 99, 1-110.
- Deshpande, S.S. & Devanandan, M.S. Reflex inhibition of monosynaptic reflexes by stimulation of type J pulmonary endings. *J. Physiol.* (1970), 206, 345-357.
- Eckenhoff, J.E. & Comroe, J.H. Jr. Blocking action of tetraethylammonium on lobelin-induced thoracic pain. *Prof. Soc. exp. Bio. Med.* (1951). 76, 725-726.
- Fowler, W.S. Breaking point of breath-holding. *J. Appl. Physiol.* (1954). 6, 539-545.
- Ginzler, K.H. & Eldred, E. Reflex depression of somatic motor activity from heart, lungs and carotid sinus. In *Respiratory Adaptation Capillary Exchange and Reflex Mechanisms*, ed. Paintal, A.S. & Gill-Kumar,

- (1977) P. pp. 358-394 Vallabhbbhai Patel chest institute Delhi
- Holmes, G. The Croonian lectures on the clinical symptoms of cerebellar disease and their interpretation. *Lancet*, (1922) 2 : 111-115.
- Jain, S.K., Subramanian, S. Julka, D.B. & Guz, A. Search for evidence of lung chemoreflexes in man: study of respiratory and circulatory effects of phenyldiguanide and lobeline. *Clin. Sci.* (1972) 42,163-177.
- Killian, K.J. & Campbell, E.J.M. Dyspnoea. In *The Thorax Part B. Lung Biology in Health & Disease* vol. 29. Ed. Roussos C. & Macklem, P.T. (1985). pp 787-828, Marcel Dekker Inc. New York.
- Korpas, J. R Tomori, Z. Cough and other respiratory reflexes. *Prog. in Resp. Res.* (1979) 12, 1-356.
- Laszlo, G. Respiratory medicine. In *Modern Medicine*. ed. Read, A.E., Barrett, D.W. & Langton Hewer, R. (1984) pp. 361-416. Pitman Medical Publishing Co. Ltd. Tunbridge Wells.
- Lepkowski, W. Questions persist about cyanide poisoning in Bhopal disaster. *Chem. & Engn. NCHS* 14, (1985) 63 (41) 42-43.
- Lilienfeld, A. & Berliner, K. Duplicate measurements of circulation time made with the alpha lobeline method. *Arch. int. Med.* (1942), 69, 739-745.
- McCloskey, D.M. Corollary discharges: motor commands and perception In *Handbook of Physiology. The Nervous System: Motor Control Vol. II Part II*. Eds. Brookhart, J.M. & Mountcastle, V.B. (1982) pp. 1415-1447. American Physiological Society Bethesda.
- Mithoefer, J.C. Lung volume restriction as a ventilatory stimulus during breath holding. *J. appl. Physiol.* (1959). 14, 701-705.
- Paintal, A.S. Mechanism of stimulation of type J pulmonary receptors. *J. Physiol.* (1969) 203, 511-532.
- Paintal, A.S. The mechanism of excitation of type J receptors, and the J reflex, In *Breathing: Hering-Breuer Centenary Symposium*, ed. Porter, R. (1970) pp. 59-71. Churchill : London.
- Paintal, A.S. Vagal Sensory receptors and their reflex effects. *Physiol. Rev.* (1973), 53, 159-227.
- Paintal, A.S. Thoracic receptors connected with sensation. *Br. Med. Bull.* (1977a) 33, 169-174.
- Paintal, A.S. The nature and effects of sensory inputs into the respiratory centres. *Fed. Proc.* (1977b) 30, 2428-2432.
- Paintal, A.S. Localization of the sensations produced by J receptors. (J area). *Proc. Int. Union Physiol. Sci.* (1983a). 15, 245.
- Paintal, A.S. The central effects of J receptors. *Proc. int. Union Physiol. Sci.* (1983b), 15, 290.
- Paintal, A.S. Lung and airway receptors. In *Control of Respiration*, ed. Pallot, D.J. (1983c), pp 78-107. Croom Helm: London.
- Paintal, A.S. High altitude studies (Mountain preservation and prosperity). *Current Sci.* (1985) 54, 119-122.
- Paintal, A.S. The visceral sensations—some basic mechanisms. *Progress in Brain Research* (1986a) 67; 3-19. In press.
- Paintal, A.S. The sensations produced by J receptors. *Bratisl. Lek. Listy*, 4 (1986b) pp (In press. In Slovak language).
- Raj, H. Sensations and reflex effects produced by J receptors in man. M.D. Thesis, Delhi University. (1984).
- Sant, Ambrogio, G. & Remmers, J.E. Reflex influences acting on the respiratory muscles of the chest wall. In *the Thorax, Part A. Lung Biology in Health & Disease* (1985) vol. 29. ed. Roussos C. & Macklem, P.T. pp 531-594. : Marcel Dekker Inc. New York.
- Stern, S., Bruderman, I. & Braun, K. Localization of lobeline sensitive receptors in the pulmonary circulation in man. *Am. Heart J.* (1966) 71, 651-655.
- Trzebski, A. Respiratory reflexes. In *Control of Respiration*, ed. Pallot, DJ. (1983) pp. 108-156. Croom Helm London.
- Widdicombe, J.G. Respiratory reflexes from the trachea and bronchi of the cat. *J. Physiol.* (1954). 123, 55-70.
- Widdicombe, J.G. Reflex control of breathing. In *MTP International Review of Science, Physiology, Series one. Vol. 2, Respiratory Physiology*, ed. Widdicombe, J.G. (1974) pp 273-301. Butterworths: London.

THREE CHEMOTHERAPY STUDIES OF TUBERCULOUS MENINGITIS IN CHILDREN*

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C.V. RAMAKRISHNAN AND S.P. TRIPATHY

Summary: Chemotherapy studies were undertaken in 180 patients with tuberculous meningitis. They were treated for 12 months with 3 regimens: the first consisted of streptomycin, isoniazid and rifampicin daily for the first 2 months, followed by ethambutol plus isoniazid for 10 months; in the second, pyrazinamide was added for the first 2 months, and in the third, rifampicin was reduced to twice weekly in the first 2 months. In the first regimen alone, streptomycin was also given twice weekly from the third to the sixth month. Steroids were prescribed for all the patients in the initial weeks of treatment. Approximately 50% of the patients were aged less than 3 years. On admission, 13% of the patients were classified as stage I, 77% as stage II and 9% as stage III. Cerebrospinal fluid (CSF) culture results were available for all the 180 patients and *M. tuberculosis* was isolated in 59 (33%). CSF smear results for acid fast bacilli were available only for the 103 patients admitted to the second and the third studies, and of these, in 60 (58%) the CSF was positive either by smear or culture.

The response to therapy was similar in the 3 studies. Despite administration of rifampicin for 2 months, the mortality was high. In all, 27% of the patients died of tuberculous meningitis, 39% had neurological sequelae and 34% recovered completely. There was a strong association between the stage on admission and the mortality rate, the deaths being highest in stage III. In the first study; when isoniazid was prescribed daily in a dosage of 20 mg/kg, 39% of the patients developed jaundice however, when the dosage was reduced to 12 mg/kg, the incidence was only 16%. In the third study, where rifampicin was administered twice a week, the incidence of jaundice was low (5%).

Introduction

Meningitis is the commonest cause of death from tuberculosis in children. While combinations of bactericidal and sterilising drugs like streptomycin, isoniazid, rifampicin and Pyrazinamide have been found to be highly effective in the treatment of pulmonary tuberculosis in adults, information about the value of these drugs in the treatment of tuberculous meningitis is limited. Three consecutive studies were therefore undertaken by the Tuberculosis Research Centre, Madras, in collaboration with the Institute of Child Health and Hospital for Children, Madras, to evolve suitable regimens for the treatment of tuberculous meningitis in children. Preliminary findings of part of the first study have already been published (Rama-chandran, 1980). A complete report of the 3 studies, including a 1 year follow-up, is presented here.

Plan and conduct of the studies

In all, 180 patients with tuberculous meningitis, aged between 1 and 12 years, who had received not more than 4 weeks of anti-tuber-

culosis treatment and had no evidence of renal or liver disease, were admitted to the 3 consecutive studies. The majority of patients belonged to the lower socio-economic groups and came from the urban and semi-urban areas of Madras city, while a few came from rural areas. On admission, 53% of the patients were aged less than 3 years [table 1]; only 17% were aged 5 years or more. Approximately half (53%) were males.

Criteria for diagnosis

The diagnosis was based on clinical symptoms and signs, notably fever, vomiting, irritability, apathy, refusal to play, anorexia, constipation, well-marked meningeal signs, impaired consciousness, coma and widespread paralysis. The cerebrospinal fluid [CSF] findings were also taken into consideration.

Investigations

A 1 TU Mantoux test (PPD batch RT 23 with Tween 80) was done on admission, and read at 2 or 3 (occasionally 4) days. Antero-posterior chest radiographs were taken on ad-

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mission and at the end of treatment. Urine tests for acetylisoniazid, bile salts, bile pigments, urobilinogen, albumin and deposits were done on admission and at 1 and 2 months; then, after, tests for albumin and acetylisoniazid were done every month. Estimations of serum aspartate, alanine amino-transferase and alkaline phosphatase activities, serum bilirubin, blood urea, plasma creatinine, haemoglobin, blood platelet count and total and differential white blood cell counts were done on admission, at 1 and 2 months and the end of chemotherapy. Biochemical, cytological and bacteriological examinations of the CSF were done on admission and every 2 weeks during the first 2 months and subsequently every month until the results were normal.

Stage I: Patients were conscious and had mainly non-specific symptoms, with or without signs of meningeal irritation, but no focal neurological signs. Diagnosis was established mainly on CSF findings.

Stage II: Patients were mentally confused and/or had neurological signs.

Stage III: Patients were comatose and had gross neurological signs.

Chemotherapeutic regimens

All patients were to be treated for 12 months. The regimens in the 3 studies were as follows:

First study: Regimen I: 2SHR/4S₂EH/6EH: Streptomycin plus isoniazid plus rifampicin daily for 2 months, followed by ethambutol plus isoniazid daily supplemented by streptomycin twice a week for 4 months, followed by etham-butol plus isoniazid daily for 6 months.

Second study: Regimen III: 2SHRZ/IOEH: Streptomycin isoniazid plus rifampicin plus pyrazinamide daily for the first 2 months, followed by ethambutol plus isoniazid daily for 10 months.

Third study: Regimen III: 2R₂SHZ/IOEH: Streptomycin plus isoniazid plus pyrazinamide dully and rifampicin twice a week for the first 2 months, followed by ethambutol plus isoniazid daily for 10 months

The streptomycin dosage was 40 mg/kg body-weight, rifampicin 12 mg/kg, ethambutol 17.5 mg/kg and pyrazinamide 30 mg/kg. The first 28 patients received isoniazid in a daily dosage of 20 mg/kg, a dose used by most paediatricians for the treatment of tuberculous meningitis. However, a substantial proportion of the patients developed jaundice during the initial phase of treatment with isoniazid and rifampicin. Consequently, the dosage of isoniazid was reduced to 12 mg/kg and this dosage was prescribed to patients admitted to the second and third studies, also. In addition to anti-tuberculosis chemotherapy the patients received supportive therapy (intravenous fluids, anti-oedema measures, anti-convulsants, vitamins etc.). As a general policy, corticosteroids were administered to all the patients for a period of 6-12 weeks. Seriously ill patients (stages II and III) were given dexamethasone by the intramuscular route in a dosage of 2-4 mg every 6-8 hours for the first 3 or 4 days followed by oral prednisolone (1-2 mg/kg bodyweight).

General management

Patients were hospitalised for the first 2

TABLE I
Distribution of patients according to age on admission

Age(year)	Patients	
	No.	%
1----	56	31
2-	39	22
3-	30	17
4-	25	14
5-	12	7
6-	9	5
7-	3	5
8-	4	
9-	1	
10-	1	
Total	180	101

Classification according to stage of disease on admission

At the time of admission, patients were examined in detail with special reference to the nervous system and were classified into 3 stages, adopting the following classification which is a modification of the one used by the British Medical Research Council [1948].

months of treatment. Those who were discharged during the first 2 months attended as out-patients daily for chemotherapy until they completed 2 months. After 2 months the patients attended twice or once a week (or once in 15 days if they lived outside Madras) to collect a supply of drugs. Their medication was fully supervised on the days they attended. Progress was assessed mainly by monthly clinical examination including a detailed neurological examination, and if indicated, a CSF examination. The patients were followed up for 12 months after completion of therapy.

Surgery

Patients clinically diagnosed to have developed hydrocephalus were investigated, and surgery (ventriculo-peritoneal shunt) was performed, if indicated.

Bacteriological procedures

CSF specimens were examined by fluorescence microscopy and cultured on Lowenstein-Jensen medium with and without pyruvate, a selective 7H11 medium with antibiotics and liquid Kirchner medium [Allen et al, 1983]. Tests of sensitivity to streptomycin, isoniazid [Tuberculosis Chemotherapy Centre, Madras 1960], rifampicin [Tuberculosis Research Centre, Madras 1983] and ethambutol [Subbammal et al, 1978] were performed. All positive cultures were identified [Marks, 1976 and Venkataraman et al, 1977].

Definitions of drug resistance

Streptomycin: A resistance ratio (RR) of 8 or more on 1 culture, or 4 followed by 8 or more on a repeat test.

Isoniazid : (a) Growth (defined as 20 colonies or more) on 1 mg/1 or a higher concentration, or growth on 0.2 mg/1 followed by the same result on a repeat test.

Rifampicin ; Growth on 64 mg/1
Ethambutol; Growth on 4 mg/1.

Results

In all, 180 patients were admitted to the 3 studies. Of these, 77 patients were treated with regimen I (first study), 29 with regimen II (second study) and 74 with regimen III (third study). A tuberculin test with 1 TU yielded an induration of 10 mm or more in 50% of the patients. In all, 84 (47%) patients had a history of contact with a known case of pulmonary tuberculosis and 99 (55%) had an abnormal chest radiograph suggestive of pulmonary tuberculosis. On admission, 24 (13%) patients

were classified as stage I, 139 (77%) as stage II and 17 (9%) as stage III. There was a suggestion that the stage of the disease on admission was related to the age. Thus, the proportion of patients with stage II or stage III disease was 115 (92%) of 125 in children aged 3 years or less compared with 41 (75%) of 55 in those aged 4 years or more ($P < 0.01$). A CSF protein value of more than 40 mg/100 ml on admission was observed in 96% of the patients. The nutritional status of the patients was very poor. Using growth standards set up by the Indian Council of Medical Research (Reddy et al 1976), only 2% of the patients were considered normal, while 64% had mild to moderate malnutrition and 34% severe malnutrition, based on deficit in weight for age [I.C.M.R. 1972].

CSF smear results for acid fast bacilli were available for the 103 patients in the second and third studies only. Of these, in 24 (23%) smear alone was positive, in 12 (12%) both smear and culture were positive and in 24 (23%) culture alone was positive. Thus in the 103 patients for whom both smear and culture results were available, the diagnosis was bacteriologically confirmed in 58%. Of the 180 patients, *M. tuberculosis* was isolated from the CSF in 59 (33%) patients, 9 of 24 stage I, 43 of 139 stage II and 7 of 17 stage III, the proportions in the different stages being similar. Of these 59, the culture was positive on admission in 46 patients, within 2 months in 11 and at 4 and 8 months in 2. Sensitivity test results for streptomycin, isoniazid and rifampicin were available for 56 patients and for ethambutol in 48 patients. The cultures were resistant to streptomycin in 1 (2%), to isoniazid in 3 (5%), to ethambutol in 1 (2%) and to both streptomycin and isoniazid in 9 (16%). All the cultures were sensitive to rifampicin.

Response to treatment

Of the 180 patients admitted to the three studies, 3 died of non-tuberculous causes and 21 were discharged against medical advice before completing the therapy (see page 61). On follow up of these discharges, 7 were reported to have died within 1 week of discharge. Since the general condition of all the 7 was very poor and the cause of death was most likely to be tuberculous meningitis, they were included in the analysis. The analysis of response to treatment was therefore based on 163 patients.

The neurological sequelae were classified as follows: Mild residual damage implied such sequelae as hyperactivity, irritability, mild perceptual defects and limited motor impairment such as facial paresis or monoparesis. Moderate residual damage included such defects as hemiparesis, involuntary movements and substantial

mental impairment. Patients with severe residual damage usually remained unconscious and even if consciousness was regained, they were incapable of independent existence.

Table II gives the response to treatment in the 3 studies. It can be seen that 27% of the 163 patients died of tuberculous meningitis, 39% had neurological sequelae (including 7% with severe sequelae) and 34% made a complete recovery. The results in the 3 studies were similar.

Table III gives the response according to the stage of the disease on admission. There was a clear association between the stage on admission and tuberculous deaths, the mortality being 9% for stage I patients, 25% for stage II and 73% for stage III. Conversely, 78% of stage I patients recovered fully, compared with

29% of stage II and 7% of stage III. An interesting finding was that, in both the stage I patients who died and the one who had severe neurological sequelae, *M. tuberculosis* was grown in CSF, the strains being resistant to both streptomycin and isoniazid. There was no association between the age of the patient and tuberculous deaths (Table IV).

Of the 44 deaths, 17 (39%) occurred in the first week, 7 being from amongst the 15 stage III patients (Table V). In all, 29 (66%) died within 4 weeks, 5 (11%) in the second month, 4 (9%) in the third month, 4 (9%) between the fourth and the sixth month and 2 (5%) between the seventh and the twelfth month. The last available CSF result was biochemically abnormal in 41 of the 44 (and bacteriologically positive in 11). The other 3 patients, who died in the fifth,

TABLE IV

Tuberculous deaths related to age on admission

Age(years)	No. of Patients	TB deaths	
		No.	%
1—	49	16	33
2—	37	8	22
3 _	29	7	24
4—	21	6	(29)*
5 _ .	12	4	(33)
6—	9	}	
	2		
	3		
	1		
	163		

Hydrocephalus: Fourteen patients (2 stage 1, 10 stage II, 2 stage III) were suspected of having developed hydrocephalus. Of these, 1 died before investigations could be carried out and in 5, permission for investigations was refused. Of these 5, 3 died (in the fourth, seventh and ninth months), while the remaining 2 had moderate and severe neurological sequelae respectively at the end of chemotherapy. The diagnosis of hydrocephalus was confirmed in the remaining 8, and 7 of these underwent surgery, a ventriculoperitoneal shunt (3 in the second, 1 in the third, and 3 in the twelfth month of treatment). At the end of chemotherapy 1 (stage I) of the 7 had complete recovery, 3 (I stage 1, 2 stage II) had moderate sequelae, 2 (both stage II) had severe sequelae and 1 (stage III) had died of tuberculosis. The eighth patient (stage II), who did not have surgery, was reported to be alive at 24 months with mild sequelae.

Blindness and optic disc changes ; Sixteen patients developed varying degrees of pallor of the optic discs while on treatment (5 while receiving isoniazid plus ethambutol). Six of these died before completing the treatment. The remaining 10 recovered and had normal fundus findings and vision at 24 months.

*Figures in brackets indicate percentages based on a total fewer than 25.

seventh and ninth months had severe neurological sequelae with normal CSF findings.

There was no association between drug resistance and response to treatment but the numbers were small (Table VI).

Twelve patients developed optic atrophy with blindness (7 during treatment with ethambutol plus isoniazid) which persisted until the end of chemotherapy. On follow up, 7 patients had died and the remaining 5 continued to have optic atrophy and blindness at 24 months.

Four patients had developed cortical blindness during the first month of therapy; all of

TABLE V *Interval between admission and*

death, according to stage of disease on admission

Stage of disease	No. in analysis	Tuberculous deaths									
		Total	Week of treatment				Month of treatment				
			1	2	3	4	2	3	4	5-6	7-12
I	23	2	1	0	0	0	0	0	1	0	
II	125	31	9	4	3	3	4	4	3	1	
III	15	11	7	2	0	0	1	0	0	1	
All	163	44	17	6	3	3	5	4	4	2	

TABLE VI

Culture and sensitivity results related to response to treatment

Initial culture/sensitivity findings	Total	TB death		Complete No.	Recovery %
		No.	%		
Culture negative	108	30	28	40	37
Sensitive to S, H and R	39@	8	21	12	31
Resistant to S,H or SH	13*	5	(38)**	3	(23)
Sensitivity test result not available	3	1	(33)	0	(0)

@ 1 patient had resistance to ethambutol alone.

*Of these, 1 had resistance to streptomycin, 3 to isoniazid and 9 to both drug

**Figures in brackets indicate percentages based on a total fewer than 25.

them regained their vision by the end of 4 months.

Of the 12 patients (aged between U—7 years) who developed ocular complications during treatment with ethambutol plus isoniazid, in the first 9, treatment with ethambutol was

subsequent 3 patients, to be on the safe side, ethambutol was discontinued and PAS substituted.

In the remaining 20 patients, who developed the ocular complications in the first 2 months of therapy with streptomycin, isoniazid and rifampicin, ethambutol was given in the continuation phase.

Discharge against medical advice

In all, 21 patients were discharged against medical advice before completion of treatment, 15 in the first phase of therapy and the remaining 6 subsequently.

Of the former 15, 2 could not be traced. Twelve patients were reported to have died; 7 within 1 week of discharge, 1 in the second week, 1 in the third week, 1 in the second month, 1 in the third month and the last, 6 months after discharge. The last 2 patients had received anti-tuberculosis treatment from other sources after discharge. The thirteenth patient (stage I on admission), whose condition was good at the time of discharge, was found to be alive 24 months after admission, with no sequelae.

Of the remaining 6 patients (all stage II), 3 were discharged during the third month (on

follow-up, 2 had died within 2 months of discharge and 1 was alive with moderate sequelae at 24 months) and 2 during the fourth month (on follow-up, 1 had severe sequelae and the other could not be traced). The sixth patient, who was discharged in the sixth month, was reported to have died 6 months after discharge: the cause of death may not have been connected with meningitis, as she had very good clinical improvement and the CSF findings were normal at the time of discharge. Death was attributed to tuberculous meningitis in the others.

Non-tuberculous deaths

Three patients (all stage II) died from non-tuberculous causes. One died in the fifth month, possibly due to an anaphylactic reaction after an injection given by a private practitioner for fever and respiratory infection. The other 2 died during the ninth month: the first due to diarrhoea with dehydration; the second developed vomiting of sudden onset and died at home the next day. Since the clinical improvement was substantial and the last available cerebrospinal fluid findings were normal, the cause of death is unlikely to have been tuberculosis in either.

Adverse reactions

This analysis is based on all the 180 patients admitted to treatment.

Jaundice: This was the major problem in the first 2 studies. In all, 30 patients developed jaundice in the 3 studies, all except 1 during the first 2 months, most of them in the second and third weeks (Table VII).

TABLE VII
Incidence of jaundice in the first 2 months*

Study	Regimen	INHdose (mg/kg)	Total patients	Patients who developed jaun- dice		Week of onset of jaundice					
				No	%	1	2	3	4	5	6-8
First	2SHR/4S ₂ EH/6EH	20	28	11	39	1	4	5	0	1	0
	2SHR/4S ₂ EH/6EH	12	49	8	16	1	2	4	1	0	0
Second	2SHRZ/10EH	12	29	6	21	0	4	1	0	1	0
Third	2R ₂ SHZ/10EH	12	74	4	5	1	0	3	0	0	0
All			180	29	16	3	10	13	1	2	0

*One other patient (.first study) developed jaundice in the fifth month.

In the first study, when isoniazid was administered in a dosage of 20 mg/kg, the incidence of jaundice was 39% of 28; when the dosage was 12 mg/kg, the incidence was much less, namely, 16% of 49. In the second study, where pyrazinamide (30 mg/kg) was added to streptomycin, rifampicin and isoniazid (12 mg/kg), the incidence of jaundice was 21 % of 29. In the third study, the same drugs as in the second study were administered but rifampicin was given only twice a week; the incidence of jaundice with this regimen was low, namely 5% of 74.

In the patients who developed jaundice, rifampicin (first study) or both rifampicin and pyrazinamide (second and third studies) were discontinued while the other drugs were continued.

Of the 29 patients who developed jaundice during the first 2 months of therapy, 24 recovered fully, the liver function test results returning to normal; however 6 of these patients died subsequently due to tuberculous meningitis. The other 5 had died while still jaundiced. Of these, 1 patient died on the day jaundice was noticed and a definite cause of death could not be determined; 2 died while recovering from jaundice with the serial liver function test values showing considerable improvement, and death was attributed to tuberculous meningitis, jaundice being a complicating factor. The fourth patient had, in addition to tuberculous meningitis, miliary tuberculosis, enteric fever and herpes, and died of hepato-cellular failure. In the last patient, jaundice persisted up to the time of death, 10 days after terminating rifampicin and pyrazinamide; a diagnosis of viral hepatitis could not be excluded.

Only 1 patient developed jaundice after 2 months (in the fifth month) while on isoniazid and ethambutol, and was diagnosed as a case of viral hepatitis. This patient recovered fully with empirical treatment.

Skin reactions : Two patients, 1 in the first and the other in the third study developed skin reactions, both in the first month of treatment. The first patient developed extensive morbiliform eruptions with crusting and exfoliation. Rifampicin was stopped and the patient recovered completely. The second patient developed vesicular eruptions over the lower abdomen and groins. All anti-tuberculosis drugs were withheld for 1 week and the patient recovered fully. The treatment was resumed uneventfully,

Arthralgia: One patient in the second study developed swelling of the elbow and knee joints during the first month. Pyrazinamide was stopped and the swelling diminished during the next 3 weeks. He could not be followed up further as he died of tuberculous meningitis.

Treatment continued beyond 12 months

Of the 163 patients in the analysis of efficacy, 119 completed treatment. In 23 of these, anti-tuberculosis treatment was continued beyond 12 months for the various reasons given below. The extended period of therapy was 1-6 months in 12 patients, 7-12 months in 10, and 24 months in 1 patient.

(a) *CSF abnormality, surgery or neurological complications*: Anti-tuberculosis treatment was continued on the advice of neuro-surgeons in

9 patients of whom 5 underwent a ventriculo-peritoneal shunt. Two others had only raised CSF protein values and in the remaining 2, the parents refused permission for investigations in ! and surgery for hydrocephalus in the other. Of the 9 patients. 4 died in the thirteenth, fourteenth, fifteenth and twenty-third months and all had severe sequelae with normal CSF findings. Considering the 5 patients with a raised CSF protein value, in 3 the CSF values became normal, at the fifteenth, twenty-second and twenty-third months while in the other 2, the high values persisted until the twenty-fourth month. The neurological status of the 5 patients alive at 24 months was as follows: 1 had severe sequelae. 2 moderate and 1 mild, while the last patient recovered fully,

(b) *Persistence of abnormality on chest radiograph:* In 72 of 119 patients who completed treatment, the chest radiograph was abnormal on admission. At 12 months, the lesions had cleared completely in 47, while there were calcified lesions in 15; in 1 patient the radiograph could not be repeated. In the remaining 9 patients, the radiographic shadows did not clear completely. In 1 patient, who had a normal radiograph on admission, an abnormality (enlargement of the carinal gland) was detected at the end of therapy. In this, and the 9 patients with persistent abnormality, anti-tuberculosis treatment was continued beyond 1 year. The CSF became biochemically normal and bacteriologically negative in all the 72 patients during the course of the 12 months.

(c) *Spinal lesions:* Two patients had spinal tuberculosis in addition to tuberculous meningitis (diagnosed on admission on one and detected in the sixth month in the other). In both, chemotherapy was prolonged on the advice of the orthopaedic surgeon. The CSF at the end of 12 months was normal biochemically as well as bacteriologically in both the patients. At 24 months, both the patients had made a complete recovery.

(d) *Other reasons:* In 2 patients it was considered inadvisable to stop anti-tuberculosis treatment at the end of 1 year on account of severe respiratory infection in 1 patient with severe sequelae (the patient died, in the twenty-first month), and the detection of pulmonary tuberculosis in one of the parents of the second (patient was alive with moderate sequelae at 24 months),

Status at 24 months

There were 119 survivors at the end of 12 months—12 with severe sequelae, 36 with moderate sequelae, 16 with mild sequelae and 55 with complete recovery.

Of the 12 patients who had severe sequelae, 5 died, in 6 the condition remained the same and 1 had improved (to moderate sequelae). Of the 36 patients with moderate sequelae, 3 died (2 of sequelae and 1 of non-tuberculous cause), 17 showed no improvement in neurological status, 13 showed slight improvement, 1 improved to mild sequelae, while the remaining 2 recovered completely. Of the 16 patients with mild sequelae, the status remained the same in 13. 1 showed slight improvement and the remaining 2 recovered completely. In the complete recovery group of 55 patients, 1 died from a complication of typhoid fever (perforation of the gut) while the recovery was maintained in the remaining 54 patients.

The survivors at the end of 24 months are being followed, up further.

Discussion

The results of the present studies show a direct relationship between the stage on admission and death from tuberculous meningitis, the proportions being 9% for stage I patients, 25% for stage II and 73 % for stage III. Similar observations have been made by others (Smith 1964, Sister Gabriel, 1979 and Girgis et al, 1976, 1978). These results suggest that early diagnosis and initiation of therapy is more important than the choice of drug regimen.

Ethambutol has been used in the treatment of childhood tuberculosis in India [Mankodi et al, 1970. Bhatia et al, 1975 and Dingley et al, 1974]. In all these studies, the dosage employed was 25 mg/kg for 2-3 months followed by 15 mg/kg, and the reported incidence of ocular toxicity was negligible. In a study comparing different ambulatory regimens for spinal tuberculosis in Korea, 45 children (aged between 1 and 15 years) were treated with ethambutol ((5-25 mg/kg) plus isoniazid daily for 9 or 18 months. All the patients were assessed monthly and tests for visual acuity, colour vision and macular thresholds and visual fields were undertaken. There was no evidence from any of the assessments in any patient of ocular toxicity due to ethambutol (unpublished data from MRC Working Party on Tuberculosis of the Spine—Personal communication from Prof. Wallace Fox). A study by Leibold [1966] suggests that, on a short term basis it is safe to prescribe as much as 45 mg/kg. In the present series of studies, ethambutol was used in a dosage of 17.5 mg/kg, a dose unlikely to cause retrobulbar neuritis. Optic chiasmatic-arteriovenous fistulae resulting in visual impairment or even blindness, with or without associated hydrocephalus, is a common complication of tuberculous meningitis. All 12 patients in the present studies who developed blindness with persistent optic atrophy had moderate to

severe neurological damage and this was most likely to have been, the cause of blindness.

The American Thoracic Society [1969] has recommended the systemic administration of corticosteroids in the management of tuberculous meningitis, a view which is supported by others [Lincoln et al 1963 and Kocen, 1977]. In the present series of studies, steroids were administered to all the patients as a routine.

Jaundice was a major problem in the first 2 studies, where daily therapy was given. The incidence was 39% in study I with isoniazid 20 mg/kg and 16% when the dose was reduced to 12mg/kg, and 21 % in study II where pyrazinamide 30 mg/kg was added to the regimen. Because of this high incidence of jaundice, in study III rifampicin was given only twice a week instead of daily during the first 2 months and the incidence fell to 5 %. The above findings suggest that the use of daily rifampicin (12 mg/kg) with a high dose of isoniazid (20 mg/kg) causes a high risk of hepatotoxicity in children with tuberculous meningitis. The addition of pyrazinamide did not appreciably alter the incidence of hepatotoxicity; a similar conclusion was reported by Girling [1978] in an extensive review of the literature. The rhythm of administration of rifampicin appeared to play a role, as regimens containing daily rifampicin carried a greater risk of hepatic toxicity than the regimen where it was given intermittently. Although the present series of studies were non-concurrent and conclusions call for caution, similar results observed in studies from this Centre on patients with spinal and pulmonary tuberculosis [Parthasarathy et al, 1986] support the above deductions. Other factors that could have contributed to the high incidence of jaundice in children with tuberculous meningitis have been dealt with by Parthasarathy and others [1986].

In conclusion, the results of the 3 studies show that, despite use of rifampicin-containing regimens, the mortality was high, especially in stages II and III, while the prognosis was good in stage I. This emphasises the need for early diagnosis and prompt treatment. The combination of isoniazid 20 mg/kg and rifampicin 12 mg/kg was associated with unacceptable levels of hepatotoxicity. Our findings suggest that, in view of the low hepatotoxicity, the third regimen consisting of 2 months of daily streptomycin, isoniazid and pyrazinamide plus twice weekly rifampicin followed by 10 months of daily ethambutol and isoniazid is a suitable regimen. It is also noteworthy that there were no relapses during the follow-up period, indicating that regular therapy for 12 months is adequate for the treatment of tuberculous meningitis.

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REFERENCES

- Allen, B.W., Mitchison, D.A., Darbyshire, Janet, Chew, W.W.K. and Gabriel, M.: Examination of operation specimens from patients with spinal tuberculosis for tubercle bacilli; *Journal of Clinical Pathology*, 1983, 36, 662.
- American Thoracic Society: The treatment of tuberculosis in children. *American Review of Respiratory Disease*, 1969, 99, 304.
- Bhatia, M.P. and Merchant, S.M.: Comparative study of antitubercular drugs in the management of primary complex. *Indian Pediatrics*, 1975, 12, 1197.
- Dingley, H.B. and Sehgal, K.L.: Treatment of pulmonary tuberculosis in children—A controlled study. *Indian Pediatrics*, 1974, 11, 289.
- Girgis, N.I., Yassin, M.W., Laughlin, L.W. Edman, D.C. Farid, Z. and Watten R.H.: Rifampicin in the treatment of tuberculous meningitis. *Journal of Tropical Medicine and Hygiene*, 1978, 81, 246.
- Girgis, N.I., Yassin, M.W., Sippel, J.E., Sorcnsen, K., Hassan, A., Miner, W.F., Farid, Z., and Abu El EHa, A.: The value of ethambutol in the treatment of tuberculous meningitis. *Journal of Tropical Medicine and Hygiene*, 1976, 79, 14.
- Girling, D.J. : The hepatic toxicity of anti-tuberculosis regimens containing isoniazid, rifampicin and pyrazinamide. *Tubercle*, 1978, 59, 13.
- Indian Council of Medical Research: Growth and physical development of Indian infants and children. *Technical Report Series*, 1972, 18, 26.
- Kocen, R.S.: Tuberculous meningitis. *British Journal of Hospital Medicine*, 1977, 18 136.

- Leibold, J.E. ; The ocular toxicity of ethambutol and its relation to dose. *Annals of the New York Academy of Science*, 1966, 135, 904.
- Lincoln, E.M. and Sewell, E.M : *Tuberculosis in children*. McGraw-Hill, New York, 1963, 173.
- Mankodi, N.A., Amdekar, Y.K., Desai, A.G., Patel, B.D. and Raichur, G.S. : Ethambutol in unresponsive childhood tuberculosis. *Indian Pediatrics*, 1970, 7, 202.
- Marks, J. : A system for the examination of tubercle bacilli and other mycobacteria. *Tubercle*, 1976, 57, 207.
- Parthasarathy, R., Raghupati Sarma, G., Janardhanam, B., Ramachandran, P., Santha, T., Sivasubramanian, S., Somasundaram, P.R. and Tripathy, S.P.: Hepatic toxicity in South Indian patients during treatment of tuberculosis with short-course regimens containing isoniazid, rifampicin and pyrazinamide, *Tubercle* 1986-, 67 (in Press).
- Ramachandran, P. : Chemotherapy of tuberculous meningitis with isoniazid plus rifampicin—Interim findings in a trial in children. *Indian Journal of Tuberculosis*, 1980, 27, 54.
- Reddy, V., Jagadeesan, V., Raghuramulu, N., Bhaskaram, C. and Srikantia, S.G.: Functional significance of growth retardation in malnutrition. *American Journal of Clinical Nutrition*, 1976, 29, 3.
- Streptomycin in tuberculosis trials committee, Medical Research Council. Streptomycin treatment of tuberculous meningitis. *Lancet*. 1948, 1, 582.
- Subbammal, S., Nair, N.G.K., Rudhakrishna, S. and Tripathy, S.P.: Comparison of various measures of sensitivity of *M. tuberculosis* to ethambutol. *Tubercle*, 1978, 59, 185.
- Smith, H.V.: Tuberculous meningitis. *International Journal of Neurology*, 1964, 4, 134.
- Sister Gabriel, M. : Diagnosis, treatment and results of treatment of tuberculous meningitis in Hong Kong. 'Present status of Tuberculosis, 1979', Abstracts from a symposium held at the Bury and District Post Graduate Medical Institute, 1979, 13.
- Tuberculosis Chemotherapy Centre, Madras : A concurrent comparison of isoniazid plus PAS with three regimens of isoniazid alone in the domiciliary treatment of pulmonary tuberculosis in South India, *Bulletin of the World Health Organisation*, 1960, 23, 535.
- Tuberculosis Research Centre, Madras : Study of chemotherapy regimens of 5 and 7 months' duration and the role of corticosteroids in the treatment of sputum-positive patients with pulmonary tuberculosis in South India. *Tubercle*, 1983, 64, 73.
- Venkataraman, P. and Prabhakar, R. : Niacin production test in mycobacteria: replacement of benzidine-cyanogen bromide reagent by o-tolidine cyanogen bromide, *Indian Journal of Tuberculosis*, 1977, 24, 153.

A STUDY OF CHRONOPHARMACOKINETICS OF PYRAZINAMIDE IN TUBERCULOSIS PATIENTS*

SANDHYA KULSHRESTHA**

Summary : The chronopharmacokinetics of pyrazinamide (PZN) was studied in 20 confirmed cases of pulmonary tuberculosis. A single fixed dose of 1.5 gm of PZN was administered at three fixed times viz. 7 A.M. 11 A.M. and 7 P.M. to each patient. PZN contents were estimated in the blood and PZN and Pyrazinoic acid (PZA) contents in the urine and various pharmacokinetic parameters viz: C_{max}, T_{max}, t_{1/2}, AUC, Y_d, Cl_p, Cl_r, duration of cone. >25 ug/ml, total excretion of PZN and PZA were evaluated. Wide interindividual fluctuations were noticed in the parameters and the differences observed in most of the results were not statistically significant. However, T_{max} (Time to peak cone.) when the drug was administered at 7 P.M. was delayed and was found to be highly significant, indicating slower rate of absorption when the drug was administered at night. The area under serum cone, time curve and duration of minimum effective cone. (>25 ug/ml) was also found to be greater although this was not statistically significant). It is hypothesised (hat. probably, the extent of the total absorption of PZN from gastrointestinal tract was more when drug was administered at night. However, since this study is based on a small group of patients of the same ethnic class, a study on large number of patients from different ethnic would be required to substantiate the present finding,

suffering from pulmonary tuberculosis were enrolled in the study. A written informed consent was obtained from

Pyrazinamids. (PZN) form an important component of antitubercular drug combination in short-course chemotherapy (Girling, 1984). It is recommended that all orally effective drugs should be given simultaneously once a day, preferably in the morning, for achieving better patient compliance. The time of ingestion in the morning hour will continue to be arbitrary till chronopharmacokinetics of antituberculosis drug is studied. This will provide an answer to the question regarding appropriate time of administration of a drug to ensure maximum effectiveness and least toxicity. Though clinical pharmacokinetics of various antituberculosis drugs have been reviewed (Holdings, 1984) no data on chronopharmacokinetic studies, including that of PZN, are available. Amongst all the antituberculosis drugs, pyrazinamide has best penetration into the intracellular tissue (Grossei, 1978), acidic foci and macro phages but detailed pharmacokinetics in tuberculosis patients has not been worked out. The present study has been planned and undertaken to find out the rhythmic changes in bioavailability, metabolism and excretion of PZN in relation to the circadian cycle (chronopharmacokinetics) in tuberculosis patients.

period of study in the New Delhi Tuberculosis Centre. graphic lesion in the lungs were considered as confirmed

Patients complaining of insomnia or any other kind of insomnia is known to affect the circadian rhythm in tuberculosis patients. Only those having normal renal function were included.

Patients were receiving their quota of anti-tubercular drugs before the study commenced. However, PZN was not included in the trial. All the antitubercular drugs irrespective of the class they belonged were stopped for two consecutive days during the study period.

Material & Method

Twenty patients of either sex weighing between 40-50 kg (body weight is known to affect the serum PZN concentration; Ellard- 1969)

Design of the Study

The protocol was designed in a way that each patient underwent three studies, A, B, and

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C as shown in Fig.-1. The patients were allocated to the study in a randomised crossover fashion, as would be evident from Fig. 1. PZN was administered as a single oral dose of 1.5 gm. at 7 A.M. in study A, at 11 A.M. in study B and at 7 P.M. in study C respectively. A washout period of 52-60 hours (h) was allowed between two study periods. Patients were fasted overnight in study A and the food was withheld for at least 4 hours before drug administration in study B and C. The breakfast or meals were served 30 minutes after the medication which was given under supervision with a glass of water.

Collection of Sample

Blood (2 ml) was drawn at 0 and at 2, 3, 12, 24 and 48 hours after intake of the drug. Samples were frozen till the estimation of PZN.

Before the drug was administered the patients were asked to void the bladder and, this

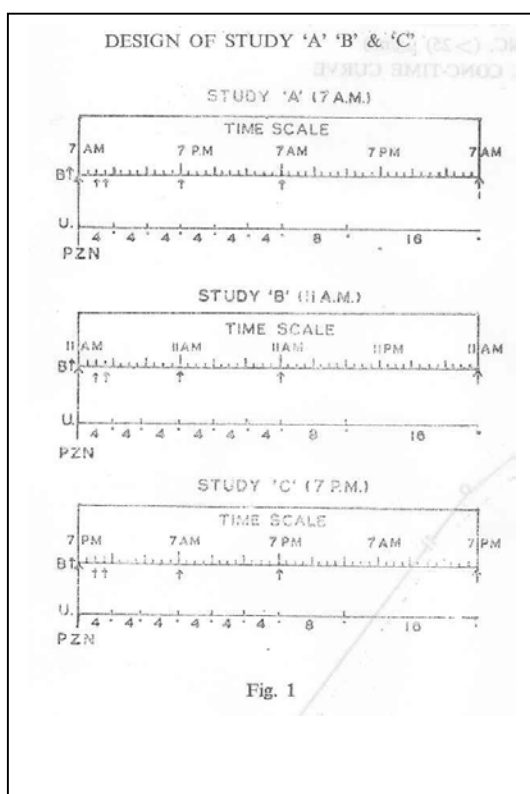


Fig. 1

Design of the Study : On each patient 3 studies A, B and C were conducted. PZN was administered at 7 AM (Study A) at 11 AM (Study B) and at 7 PM (Study C). Between studies a gap of 52-60 hours was allowed.

PZN = Pyrazinamide ingestion 1.5 g,
 B = Time of blood samples collection
 U = Periodical collection of urine sample (see text)

sample was taken as blank (Control). Thereafter, cumulative urine samples at 4, 8, 12, 16, 20, 24, 32 and 48 hours were collected after drug administration and volume of each sample was determined. The pyrazinoic acid (PZA) --a major metabolite of PZN and unchanged PZN were estimated- in these preserved samples.

Estimation of PZN and PZA

The PZN was estimated in the serum by modifying the method of Subbimal et al, (1968) (Once appendix; I), in the sense that the dowex column used by us for elution was of dimension 9x 30 mm i.e. 270 m² instead of 8 x. 40 mm U-. 320 m². This reduction in the column size did not interfere with the separation of PZN from PZA as blood contains very little amount of PZA. Rather, it saved the consumption of dowex material. Further, during standardisation we could, not detect the optional density in the second elute (5 ml) collected through the dowex column and therefore, for remaining estimation only one elute (5 ml) was collected. In modification has saved time.

The urine samples were analysed for PZN and PZA by following the method of Gurusurthy et al., 1981.

Evaluation of Pharmacokinetic Parameters

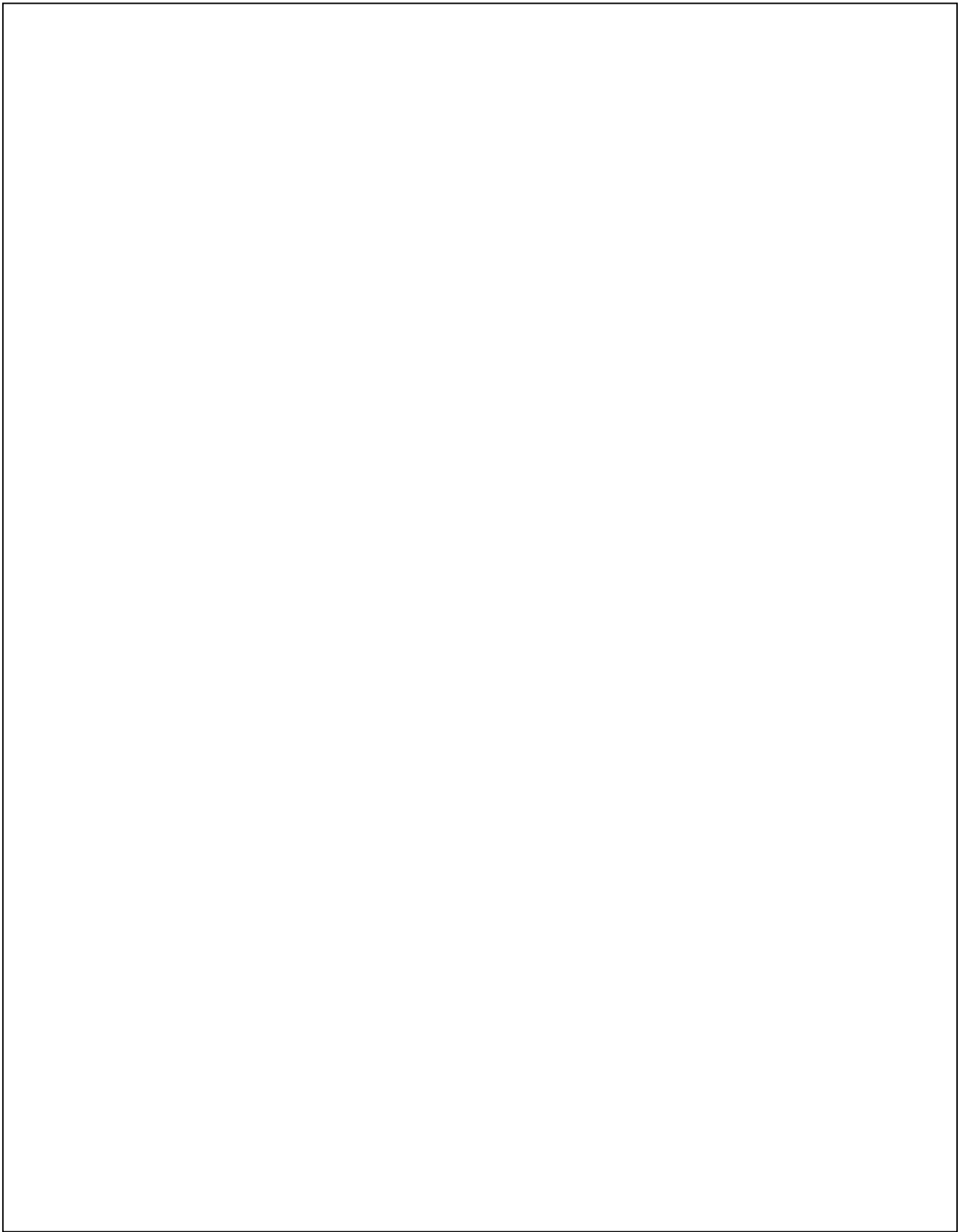
After estimating the PZN concentration in each of the blood samples, the serum values of the individual patient were plotted on the semilog scale (Y-axis) against time in hours (X-axis) and the long serum concentration-time curve was constructed. The pharmacokinetics of PZN in individual tuberculosis patients was evaluated by single compartment open model analysis. The methods employed for calculation of various pharmacokinetic parameters are as follows:-

- (a) (i) Peak Serum Concentration ('C_{max}') in ug/ml.
- (ii) Time to peak serum concentration ('T_{max}') in hours (h).
- (iii) Serum half life of PZN ('t_{1/2}') in hours (h).
- (iv) Duration of minimum effective concentration (>25 fig/ml) in hours (h).

These parameters were estimated from lining serum concentration time curve (Fig. 2).

- (h) Elimination rate constant (k_{el}) : was calculated

$$k_{el} = \frac{0.693}{t_{1/2}}$$



A STUDY OF CHRONOPHARMACOKINETICS OF PYIUZTNAMTDF IN TUBERCULOSIS PATIENTS

- (h) Total excretion of **PZA** in 24 h and 9 percentage of dose excreted during First 24 hours was calculated as above.

The values of parameters from (b) till (h) were obtained by feeding the data in the computer (IBM-360/44),

The patients were closely monitored for any untoward reaction during the entire period of study.

The data were analysed statistically by carrying out "analysis of variance" and the statistically significant difference, if any, amongst the three studies was noted. The statistical difference in T_{max} (Time to peak serum conc.) was tested by the 'Chi-square test'.

The chemicals of Sigma chemicals Co. U.S.A. Anlar/L.R. Grade/BDH/E. Merck/Sarabhai India/Lupin Laboratories were used, viz: Tnchloraeeue acid (7.5% w/v); Dowex. 1 x 8,

Chloride form, dry mesh 200-400; Sodium hydrozide (2N); Sodium nitroprusside solution (0.2%, w/v). Sodium chloride (0.5M), Standard 'PZN and PZA,

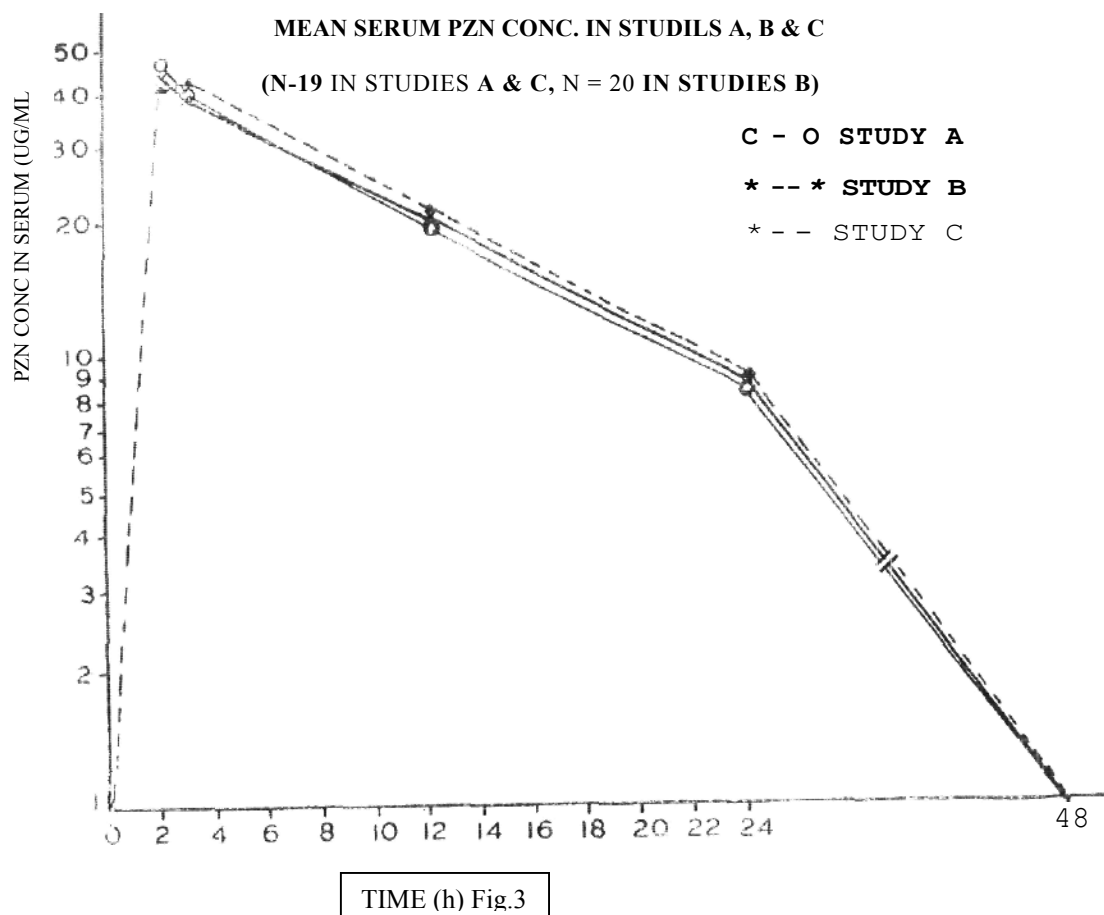
The drug PZN (ZIN—500 mg) was obtained from single source--the Radicura Pharmaceuticals Co., New Delhi,

Results

Out of twenty patients enrolled for the study, one patient could not complete the study 'A' and another patient study 'C'. These dropouts were due to personal reasons. Thus, in studies 'A' and 'C' the results of 19 patients and in study 'B' those of 20 patients have been analysed. The average age ranged between 21-54 years and the weight was between 40-50 kg. The ratio of Male : Female was 9 : 1 .

1. Serum Concentration, of PZN and 'Time to Peak'

After ingestion of a fixed dose of 1.5 gm of



PZN the mean serum conc., at 2, 3, 12 and 24 h in all the three studies was found to be not significantly different from each other (Fig.-3). Similarly the differences in the C_{max} i.e. peak serum conc., in study 'A' ($42.85 \pm \text{S.D. } 3.49$ Hg/ml) and in study 'B' ($41.86 \pm \text{S.D. } 25$ fig/ml) and in study 'C' ($42.71 \pm \text{S.D. } 3.47$ jig/ml) were not marked. The pattern of the slope of the serum concentration—time curve appears to follow exponential decline, in all the three studies the serum PZN levels were undetectable at the end of the 48 h in all the patients, except in a single patient in study 'C' who showed a small amount (2.34 ug./ml) of PZN in blood. About 75—80% of the drug was eliminated in first 24 h. Great inter-individual and inter-studies variation in the serum levels of PZN was observed, which could be the reason for statistically non-significant difference in the mean values.

After the administration of drug in the evening (7 P.M.) the time to peak serum conc. (T_{max}) was observed to be increased ($2.52 \pm \text{S.D. } 0.51$ h) which was highly significant compared to that in study 'A' ($2.15 \pm \text{S.D. } 0.37$) and study 'B' ($2.15 \pm \text{S.D. } 0.36$), ($P < 0.02$). This finding indicates that probably the rate of absorption is slow in evening hours though looking at Fig-3, it appears that the total absorption has been more in study 'C'.

2. Serum half life ($t_{1/2}$)

Again much inter-individual and inter-studies variations were found in values of $t_{1/2}$ of PZN. It ranged from 8—11.4 h in study 'A' and 6.8—10.7 h in study 'B' and 7.8 to 12.01 h in study 'C'. Though the $t_{1/2}$ in study 'B' was shorter than in studies 'A' and 'C', the difference however, was not statistically significant (Table I)

3. Elimination rate constant (K_{el}) : Area under plasma conc.-time curve (AUC_{0-∞}); Volume of distribution (V_d) ; Plasma Clearance (C_{pl}) and renal clearance (C_{lr}) :

The comparative values of each parameter with mean and S.D. determined for each of the studies 'A', 'B' and 'C' are given in Table 1. It is obvious that there is no significant difference in the values of these parameters in three studies.

The AUC_{0-∞} in study 'C' seems to be more ($675.74 \pm \text{S.D. } 83.44$ ng. h.ml) as against $637.24 \pm \text{S.D. } 76.21$ [ug.h.ml⁻¹] and $6347 \pm \text{S.D. } 108.02$ ug. h.ml⁻¹ in study 'A' and 'B' respectively. However, this difference was not statistically significant; this could be on account of large inter-individual variations which have blunted and attenuated the statistical analysis.

4. Duration of minimum effective concentration >25 ug/ml) : (Fig. 4)

The calculated period for which the minimum effective concentration lasted in each study was found to be undoubtedly longer in study 'C' ($8.86 \pm \text{S.D. } 1.82$ h) as compared to study 'A' and 'B' ($8.05 \pm \text{S.D. } 1.71$ h and $8.02 \pm$

DURATION OF SERUM PZN CONC.

(>25 fig/ml)

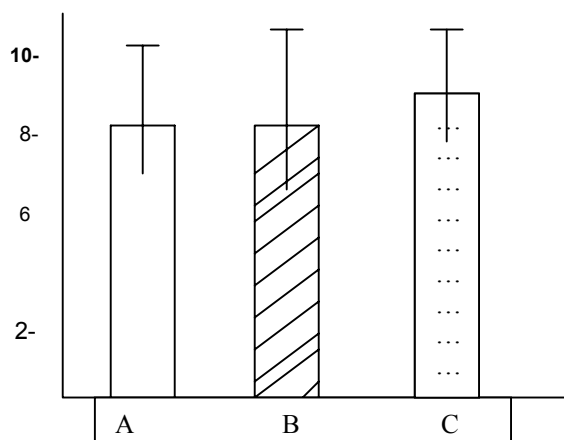


Fig. 4

For each Study the period during which Serum PZN Conc, remained above 25 ug/ml was determined (for method see fig. 7 of the text)- It is reported to be an effective antibacterial conc.

Histogram shows that it persisted for longer time in study C as compared to study A & B.

S.D. 2.10h) respectively. Again, no statistically significant difference was found in the minimum effective concentration in three studies.

A positive correlation ($r=0.72$) was observed between the peak serum concentration in individual patient and the duration of the minimum effective concentration (>25 u.g/ml) of PZN.

5. Renal elimination of PZN and PZA (Tables 2 a, (b)

The results of PZN and PZA excretion in urine are depicted in Fig.-5.

A wide variation was observed in the total amount of PZN and PZA excreted in the urine in individual patient in all the three studies.

PZN is mainly excreted in the form of its

TABLE I

Mean values \pm S.D. of various pharmacokinetic parameters in studies A, B & C

(n=19 in Studies A & C, n=20 in Study B.)

S. No.	Pharmacokinetic Parameter	Study A	Study B	Study C	P Value
1.	Peak Serum conc. (C_{max}) ($\mu\text{g/ml}$)	42.852 \pm 3.492	41.960 \pm 4.254	42.715 \pm 3.479	>0.05*
2.	Time to Peak (T_{max}) (h)	2.157 \pm 0.374	2.150 \pm 0.366	2.520 \pm 0.512	<0.02**
3.	Serum half life ($t_{1/2}$) (h)	9.978 \pm 1.001	9.430 \pm 1.226	4.978 \pm 1.135	>0.05*
4.	Elimination rate constant (K_{el}) (h ⁻¹)	0.070 \pm 0.007	0.075 \pm 0.011	0.072 \pm 0.009	>0.05*
5.	Area under plasma conc.—time curve ($AUC_{0-\infty}$) ($\mu\text{g. h.ml}^{-1}$)	637.247 \pm 76.217	634.719 \pm 108.000	675.747 \pm 83.442	>0.05*
6.	Apparent Vol. of distribution (V_d) (L)	34.259 \pm 4.484	32.864 \pm 5.174	31.881 \pm 5.481	>0.05*
7.	Plasma Clearance (Cl_p) (L/h)	2.388 \pm 0.289	2.433 \pm 0.414	2.260 \pm 0.329	>0.05*
8.	Renal Clearance (Cl_r) (L/h)	0.140 \pm 0.021	0.141 \pm 0.040	0.150 \pm 0.043	>0.05*

*Difference in Inter-studies values : Not significant.

** T_{max} in 'C' was highly significant compared to 'A' & 'B'.

TABLE 2a

MEAN (\pm S.D.) URINARY EXCRETION OF PZN AT DIFFERENT TIME INTERVALS

(n=19 in Studies A & C, n=20 in Study B)

Time after drug Administration	A		B		C	
	Total Excre. (mg)	% Excre.	Total Excre. (mg)	% Excre.	Total Excre. (mg)	% Excre.
0—4 h	12.67 \pm 2.02	0.845	13.38 \pm 2.63	0.893	14.03 \pm 2.93	0.935
4—8 h	10.30 \pm 1.69	0.689	10.76 \pm 2.06	0.717	10.62 \pm 2.24	0.708
8—12 h	8.02 \pm 2.74	0.534	7.66 \pm 1.45	0.512	9.45 \pm 3.99	0.630
12—16 h	5.21 \pm 1.68	0.347	7.16 \pm 4.79	0.477	5.80 \pm 1.72	0.386
16—20 h	4.35 \pm 1.51	0.290	6.02 \pm 3.91	0.401	5.50 \pm 2.37	0.366
20—24 h	3.28 \pm 0.78	0.218	4.35 \pm 1.90	0.290	3.70 \pm 2.08	0.246
24—32 h	4.47 \pm 4.47	0.298	3.04 \pm 0.04	0.202	4.41 \pm 2.51	0.294

TABLE 26

MEAN (\pm S.D.) URINARY EXCRETION OF PZA AT DIFFERENT TIME INTERVALS

(n=19 in Studies A & C, n=20 in Study B)

Time after drug Administration	A		B		C	
	Total Excre.	% Kxcre.	Total Excre.	% Excre.	Total EKRC.	% Excre.
	(mg)		(mg)		(mg)	
0—4 h	127.504 \pm 20.03	8.50	126.654 \pm 1.15	8.44	133.68 \pm 20.14	8.91
4—8 h	106.894 \pm 16.6?	7.12	104.83 \pm 17.26	6.98	112.46 \pm 17.75	7.49
8—12 h	84.174 \pm 19.61	5.61	79.534 \pm 5.54	5.30	98.31 \pm 38.38	6.55
12—16 h	61.124 \pm 10.61	4.07	75.82 \pm 34.12	5.5	63.60 \pm 14.88	4.24
16—20 h	50.83 \pm 15.41	3.38	73.024 \pm 3.66	4.6	57.87 \pm 26.75	3.85
20—24 h	43.07 \pm 8.37	4.20	47.06 \pm 21.13	3.13	46.084 \pm 26.23	3.07
24—32 h	49.554 \pm 6.92	3.0	47.03 \pm 18.52	3.3	54.97 \pm 34.30	3.66

metabolite PZA. while only a small amount of PZN is excreted unchanged in the urine.

in all the three studies during the first 4 h after drug administration the excretion of both PZN and PZA was maximum. It fell exponentially till 20-24 h. The major metabolite of PZN, i.e. PZA was present upto 48 h in the urine while no trace of PZN was found after 24-32 h.

The excretion of unchanged form of PZN was about 3% of the total drug administration, while its metabolite was excreted to the tune of 40% of the total drug administration.

The excretion of both PZA and PZN was more during first 12 h in study 'C' as compared to that found in study 'A' and 'B' (Fig-4), though this difference in excretion during first 12 h was also not found to be statistically significant.

On continuous surveillance for adverse reactions, three patients in study 'A', two in study 'B' and one in study 'C' complained of mild gastric irritation and abdominal discomfort. This did not warrant the stoppage of the drug. None of our patients developed any serious reaction during the entire period of the study.

Discussion

PZN is a cornerstone drug in the short course chemotherapy of tuberculosis since its penetra-

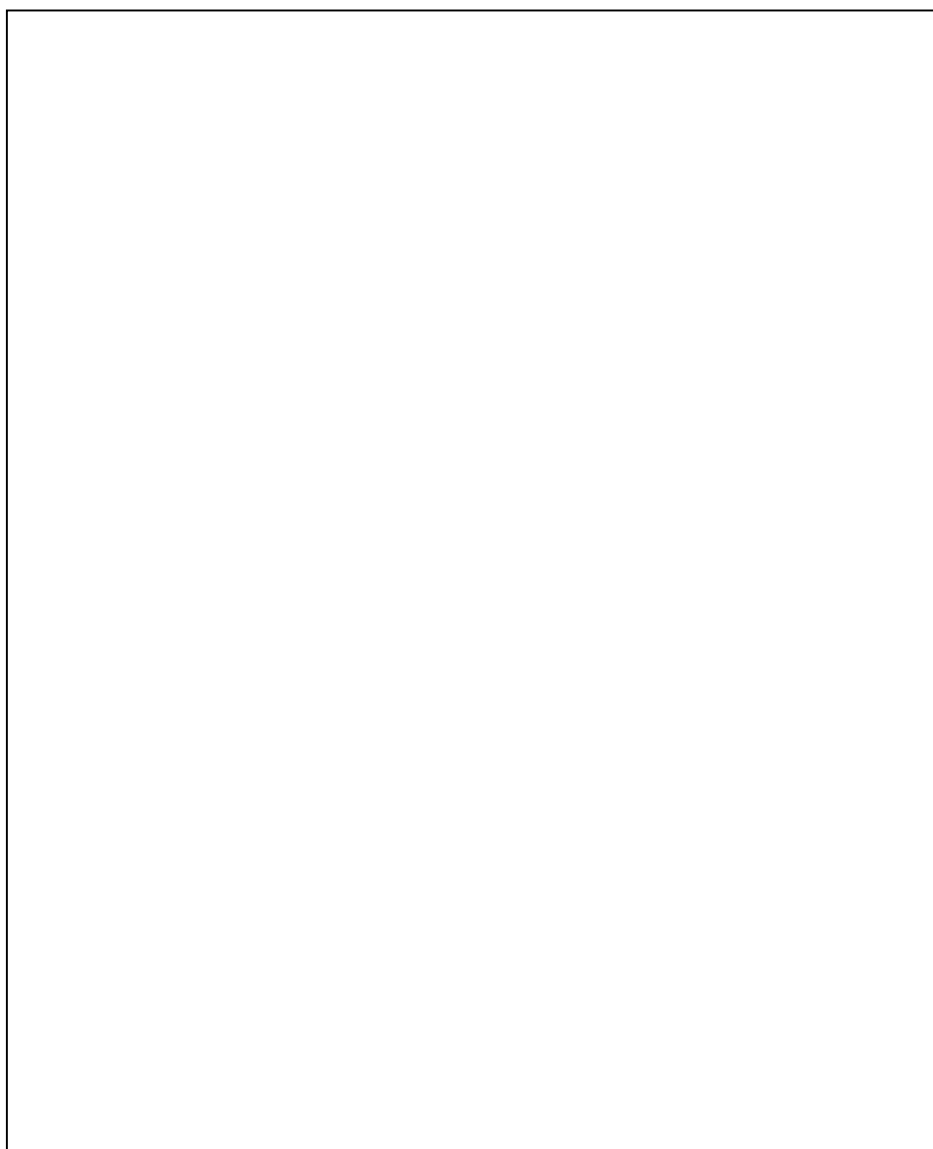
tion in the intracellular tissue is maximum and it is bactericidal. Though its pharmacokinetics has been recently reviewed (Holdiness, 1984), many of its other aspects such as volume of distribution (Vd), Plus mi clearance (Clp) and Elimination rate constant (Kel) have not yet been elucidated. Conventionally, it is administered as a single dose in the morning. In fact, most other antitubercular drugs are given concomitantly during morning hours. Is this time of administration (morning) empirical/traditional or based on chronopharmacokinetic studies? We have attempted to seek an answer to this question which has not, surprisingly, been studied till now.

The values of mean peak cone, of PZN in serum obtained in our studies ('A', 'B' and 'C') are in agreement with that reported by Carrada Bravo, 1975. The intra-studies difference in the mean peak serum cone, was minimal and insignificant. The pattern of serum cone.—time curve indicates that the drug follows single compartment model system and that the decline is exponential. The same findings were observed by EUard but his observation of peak Serum Cone, of 33 E^g/ml) was relatively lower than that estimated (42-43 ng/ml) in the present study, while Caccia, 1957 reported higher values of 45 ug/ml after a single dose of 1 grn. Much importance cannot be attached to this finding because he conducted the study only in one patient.

It is imperative that the kinetic studies must be done in a good number of subjects. Despite inclusion of nineteen to twenty patients in three of the present studies we found vast inter-individual differences in mean peak serum concentration, because in study 'A', it ranged from 39.45 to 52.4, in study 'B' 34.03 to 50.06 and in study 'C' 34.07 to 48.8 ug/ml.

The minimum effective concentration of PZN needed for antibacterial activity in the blood is reported to be >25 ug/ml. The information about the duration of this critical concentration, has been elicited after administration of a fixed dose at varying times of the day. When the drug was given at 7 P.M., the minimum effective concentration lasted for 9 h in comparison to 8 h in other situations.

MEAN RENAL EXCRETION RATE OF PZN & PZA IN THREE STUDIES
DURING DIFFERENT TIME INTERVALS



A good correlation between peak serum concentration and duration of minimal effective concentration, as reported by Subbimal, 1968 and Ellard, 1969 were also found in the present study. However, this was applicable to individual patients irrespective of the time of drug administration.

The time to achieve peak serum concentration (T_{max}) is known to be influenced by the circadian rhythm. Kyle et al. (1980) observed delayed T_{max} when Theophyllin was administered at 7 P.M. as compared to 7 A.M. Likewise, the dosing of clorazepate dipotassium (Aymard and Soullairac, 1979), Hexobarbital (Altmayer et al., 1979), and 10-hydroxy Nonrypyline (Nakino and Hollister, 1978) at 7 P.M. led to delayed T_{max} . In line with these observations, the T_{max} has been achieved at 2.53 h on ingestion of PZN at 7 P.M., which was significantly more compared to the T_{max} values of 7 A.M. and 11 A.M. administration (2.15 h). This significant finding of delayed time to peak concentration, could be due to slower rate of absorption of drug, administered at 7 P.M. The protocol was designed in a manner that the food, would not affect the absorption of drug which otherwise has been shown to alter the absorption of drug from gastrointestinal tract (Goetz et al., 1976). Since the food intake was limited and spaced equally in all the three studies and also the quantity and quality of food was almost identical after administration of drugs in each cycle, these factors are unlikely to have affected the delayed T_{max} observed in study 'C' in which the drug was given at 7 P.M. Another important factor which could influence the absorption pattern and thereby T_{max} , could be posture of the body (Halberg, 1962). In the present study the effect of body posture can be eliminated since patients in all the studies were ambulatory for at least 3 h after drug ingestion.

In respect to mean serum half life ($t_{1/2}$) of PZN, the manipulation of the time of administration of drug has not made any significant difference. However, 'Area under the serum concentration-time curve' (vide infra) after 7 P.M. administration was calculated to be greater. Wide inter-individual and inter-studies variations were observed in the serum half life of PZN in all the three studies. Not much credence can be given to $t_{1/2}$ values so far as circadian rhythm is concerned. Likewise, the mean elimination rate constant (K_{el}) was to be almost identical in all the three studies. It is worthwhile to mention here that the data on K_{el} of PZN in tuberculosis patients are not readily available, as far as we could ascertain from the literature to which we could have an access.

The determination of Area under serum concentration-time curve is an integral parameter in any kinetic study because it reflects the bioavail-

ability of the orally administered drugs. Normally, bioavailability is estimated by the formula $AUC(o) / AUC(iv)$. Non-availability of the intravenous preparation of PZN left no choice but to assume that bioavailability of the oral preparation of PZN is 100%. This assumption is supported by the finding of Ellard, 1969, who could not detect PZN traces in the stools and thus suggested that it is completely absorbed from the gastro-intestinal tract and widely distributed in the body. Taking bioavailability as 100% we calculated the apparent volume of distribution (V_d) and Plasma clearance (Cl_p) data on which are not available. However, no significant difference in these values among three studies could be detected. It appears therefore, that V_d and Cl_p remain unaffected and unaltered irrespective of the time at which the drug is administered.

Following PZN administration in the evening 7 p.m. the $AUC_{0-\infty}$ was apparently higher as compared to forenoon period, though the values were not statistically significant. As has been stated earlier, statistical calculations are found to be distorted because of the wide inter-individual variations. It is believed that AUC in study C is definitely larger. The bio-availability of PZN appears to be greater when administered in the evening. This finding is in consonance with the observation of Bucher and Reditzki, 1951, who showed that AUC of Ethanol was maximum when administered in night and also of Kyle et al., 1980 who observed that theophyllin bioavailability was greater when administered at 7 P.M. as compared to the morning dose. Thus, circadian rhythm is known to exercise an influence on the bioavailability of drugs. From these data it can be postulated that the PZN when administered in the evening (before retiring to bed) is absorbed slowly but the total quantity absorbed is enhanced, leading to larger area under curve. This also explains the delayed T_{max} .

Our finding that only 3 % of PZN is excreted and 32.37% of its metabolite i.e. PZA is excreted is in total agreement with that of Ellard (1969). However, the excretion rate of PZN and PZA was comparatively higher after evening dose ($P > 0.05$). This enhanced rate of excretion could be attributed to the change in the urinary pH as affected by the circadian rhythm. Because, during night the urinary pH is decreased and PZN being a basic drug gets ionised, resulting into decreased re-absorption and increased excretion in the urine. Nonetheless, the increased rate of absorption during first 12 h contradicts the longer duration of minimum effective concentration in patients who received the drug at 7 P.M. The total excretion of the drug remained unaffected by the time of administration of the drug. Because of these

paradoxical finding it is difficult to arrive at any conclusion. However, based on the findings of the present study it would probably be advisable to administer the PZN as a single dose of 1.5 g in at bed time in adults and that the minor untoward effects of much less frequency should not pose much problem.

REFERENCES

1. Altmayer, P., Mayer, D., Mayerback, H. Vor, Lucker, P., Rindt, W. and Wetzelsberger, F. : Circadian variations in pharmacokinetic parameters after ORAL absorption of lixobarbital. *Chronobiologia*, 1979, 6 : 73
2. Aymard, N. and Soulaire, A. : Chronobiological changes in pharmacokinetics of dipotassium chlorazepate, a benzodiazepine in Reinberg and Halberg (Eds.) *Chronopharmacology* 111-116, Pergamon Press Oxford, 1979.
3. Bucher, T. and Redetzki, H. Eine spezifische photometrische Bestimmung von Athylalkohol auf fermentative Wege. *Klin. Wschr.* 1951, 29 : 615.
4. Caccia, P.A. : Spectrophotometric determination of pyrazinamide in nude blood concentrations and excretion through the kidney. *Amer. Rev. Tuberc.* 1957. 75 - 105-110.
5. Carrad Bravo, T., Ellard, G.A., Mitchison, D.A. Horsfall, P.A.L. : Reappraisal of the activity of 1975, 56:211.
6. Conroy, R.T.W.L. and Mills, J.N. : *Human Circadian Rhythms* J & A Churchill, London, 1970.
7. Ellard, G.A. : Absorption, metabolism and excretion of pyrazinamide in Man. *Tubercle*. 1969. 50 : 144.
8. Girling, D.J. : The role of pyrazinamide in primary chemotherapy for pulmonary tuberculosis. *Tubercle*. 1984, 65 : 1.
9. Goetz, F., Bishop, J., Halberg, F., Southern, R., Brunning, R., Semke, B., Greenberg, B., Minors, D., Stoncy, P., Smith, I., Rosen, G., Cressery, D., glucafon, insulin and iron. *Experientia* 1976. 32 : 1981
10. Grosset, J. : The sterilizing value of Rifampicin and Pyrazinamide in experimental Short-course Chemotherapy. *Tubercle*. 1978, 59 : 287.
11. Gurumurthy, P., Nair, N.G.K. and Sarma, R. : Method of the estimation of pyrazinamide and pyrazinoic acid in bovine fluids. *Ind. J. Med. Res.* 1981, 71 : 129.
12. Halberg, F. : Physiologic 24-hour rhythm, a determinant of response to environmental agents. In : E Schaefer (ed.) : *Man's Dependence on the Earthly Atmosphere*, 48. The MacMillan Company, New York. 1962.
13. Holdiness, M.R. : *Clinical Pharmacokinetics of the Antituberculosis drugs*. *Clinical Pharmacokinetics*, 1984, 9 : 511.
14. Kyle, G.M., Smdensky, M.H., Thorne, L.G., His, B., Robinson, A. and McGovern, J.P. : Circadian rhythm in the pharmacokinetics of orally administered theophyllin in Smdensky et al (Eds). *Recent Advances in the Chronobiology of Allergy and Immunology*, PP. 95-111., Pergamon Press Oxford, 1980.
15. Nakano, S. and Hollister, L.E. : No circadian effect on nortryptiline kinetics in man, *Clinical Pharmacology and Therapeutics*, 1978, 23 : 199
16. Subbama, S., Risiinainiit [Iiy, D.V., Tripathy, S.P. and Venkatriaman, P. Concentration of pyrazinamide attained in serum with different doses of the drug. *Bull. W.H.O.* 1968 39 : 77).
17. Weiner, I.M. and Tinker, J.P. : Pharmacology of pyrazinamide : Metabolic and renal function studies related to the mechanism of drug induced renal retention. *J. Pharmacol. Exp. Ther.*, 1972, 180 : 411.
18. Yeh, K.C. and Kwan, K.C. : Scientific commentary. A comparison of Numerical Integrating Algorithms by Trapezoidal, Lagrange and Spline Approximation. *J. Pharmacokinetic and Biopharm* 1978, 6 : 79.

APPENDIX

METHOD OF ESTIMATION OF PZN IN SERUM

PZN in the serum was estimated by the method described by Subbamal et al. (1968), with minor modifications in the method. The serum was separated from the blood. One ml of test serum was treated with 2 ml of 7.5% Trichloroacetic acid, shaken on vortex shaker and then centrifuged at 3000 r.p.m. for 10 minutes. The protein free supernatant (1 ml extract) was sucked by the capillary pipette and was then applied to a vertical column (9 x 30 mm) of Dowex 1 x 8 chloride (200-400 mesh) prepared in water. The elution was done by repeated washing with deionised water and 5 ml of elute was collected. To this elute 0.5 ml of 2N NaOH and 0.5 ml of freshly prepared solution (0.2%) of Sodium nitroprusside was

added. The samples were left for 15 minutes at room temperature for colour to develop. The optical density of the intensity of orange-brown colour so developed in each sample was read with reference to blank serum, keeping always the wavelength at constant at 490 nm. The LKB ULTROSPEC 4050 UV-VISIBLE SCANNING spectrophotometer equipped with Apple IIe computer has been used for all estimations.

From the optical density, the concentration of PZN in the test serum was obtained by extrapolation from standard curve. The parallel standards were run with each set of test samples.

CHOICE OF SAMPLE SIZE IN SHORT-COURSE CHEMOTHERAPY TRIALS OF TUBERCULOSIS

M.C. SATAGOPAN AND S. RADHAKRISHNA*

Summary: Two approaches to computing sample size in clinical trials of short-course chemotherapy are described. One pertains to the conventional comparison situation, and it is concluded that about 1.50-200 patients with full follow-up are required on each regimen. The second approach examines whether a regimen under study is "sufficiently highly effective" for use in the programme, and in this situation about 100-125 patients with full follow-up are necessary. A review of published reports indicates that the sample sizes employed are usually inadequate.

Introduction

A development of major significance in the last decade has been the evolution of short-course regimens for the treatment of pulmonary tuberculosis (Fox and Mitchison, 1975). It is now widely known that a long-term efficacy of at least 90% can be attained if highly potent drugs such as rifampicin and pyrazinamide are combined with well-established, first-line drugs such as isoniazid and streptomycin. Even so, many clinical trials are still being undertaken by scientist in different countries, varying the drugs and dosages, the rhythm of drug administration, and the duration of treatment. The aim of these studies is to identify regimens that are effective, non-toxic, acceptable to the patient and suitable for wide-spread use. In many of these attempts, the sample size (i.e. the number of patients in each treatment group) appears to have been decided upon rather empirically, and is often statistically inadequate. The object of this study is to provide some practical guide lines for the choice of sample size in such trials.

Materials and methods

Sample size determination is usually made with the aim of ensuring that the trial is capable of demonstrating statistically the existence of a pre-specified difference in efficacy between two regimens. The required sample size then depends upon (a) the likely values of the two proportions, (b) the acceptable level of Type I error, namely, the error of rejecting the null hypothesis of the equality of the two proportions when it is true, and (c) the acceptable level of Type II error (its complement is called 'Power'), namely, the error of accepting the null hypothesis when it is untrue and an alternative hypothesis of a pre-specified difference between the two proportions is true. The technique we employed for computing the sample size is the Arc sine method with the continuity correction (Walters 1979). Here, n, the number

of patients in each group, is given by the formula

$$n = \frac{(Z_a + Z_b)^2}{2(O_1 - O_2)^2}$$

where O is the angular transform of the proportion and is measured in radians, and Z_a and Z_b are the normal deviates corresponding to specified Type I error of a (2-tail) and Type II error of b. To correct for continuity, $1/2n$ is added to the smaller proportion and subtracted from the larger proportion and n recalculated; the iterative process is continued till successive values of n coincide.

An alternative approach, especially relevant in the context of short-course regimens because they are usually highly effective, is to pose the question whether the regimen under study is of sufficiently high efficacy for recommending it for generalized use. In this situation, the required sample size depends on (a) the definition of 'sufficiently highly effective' regimen, (b) the definition of 'insufficiently highly effective' regimen, (c) the acceptable level of Type I error, a (1-tail) i.e. the risk of classifying a highly effective regimen as not highly effective and (d) the acceptable level of Type II error, b, i.e. the risk of classifying an 'insufficiently highly effective regimen' as a 'sufficiently highly effective' regimen. In this situation, the formula is given by

$$n = \frac{(Z'_a + Z'_b)^2}{4(O_1 - O_2)^2}$$

The continuity correction is employed as above, and n is calculated by an iterative process.

Results

Comparative trials

In order to have a 90% chance of detecting a 5% difference in efficacy between two regimens.

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the minimum number of patients with *complete* follow-up on each regimen must be 288, and this applies when the more effective regimen has an efficacy of 99% (Table 1). If the latter is 95% the number increases to 608, and if it is only 90% the number becomes as large as 951. If the investigator is prepared to settle for 80% 'power', the corresponding numbers are 226, 464 and 721, respectively, per regimen. Clearly, even these numbers are impracticable in most situations, and consequently it is not realistic to mount trials for detecting 5% differences in efficacy of short-course regimens. For detecting a 10% difference, the numbers required are 118-282 for 90% power, and 94-215 for 80% power. If the efficacy of the more effective regimen is of the order of 90-95 %, the corresponding numbers are 199-282 for 90% power and 153-215 for 80% power. Therefore, comparative trials must aim to ensure that a minimum of 150-200 patients

are available for analysis for each regimen. When allowances are made for drop-outs, which could be, say, 20%, over a 2-year period, the minimum intake per regimen works out to be approximately 190-250.

Trials aimed at identifying highly effective regimens

In trials whose aim is to determine whether a short-course regimen is sufficiently highly effective for recommending it in the tuberculosis programme, one should particularly guard against the danger of calling an insufficiently effective regimen as highly effective, since several known highly effective regimens are already available. For various definitions of 'sufficiently' and 'insufficiently' effective regimens (difference in efficacy between the two is taken as 10%), and for sample sizes of 100, 125, 150, . . . , 300, the risk of this type of error is set

TABLE 1

*Required number of patients with full follow-up in each treatment group**

Power	between the regimens in efficacy (%)	Efficacy of the more effective regimen (%)									
		2SS	375	456	533	608	681	751	820	837	951
90%	6	226	287	343	397	449	499	548	595	641	686
	7	185	230	272	311	349	386	422	456	490	522
	8	156	191	222	253	282	310	337	363	389	413
	9	134	162	187	211	234	256	277	298	318	337
	10	118	140	161	180	199	216	233	250	266	282
80%	5	226	290	351	409	464	519	571	623	672	721
	6	178	223	265	305	344	381	418	453	487	521
	7	146	179	210	240	268	296	322	348	373	397
	8	123	149	173	195	217	238	258	278	297	315
	9	107	127	146	163	181	197	213	228	243	258
	10	94	110	125	140	153	167	180	192	204	215

*Using the Arc sine method with continuity correction and Type I error (2-tail)=0.05.

Note: The number of patients to be admitted to each regimen can be obtained by multiplying the entry in the table with an escalation factor given by $[(100)/(100-\text{drop-out rate})]$

out in Table 2, For example, if a sufficiently highly effective regimen is defined as one having an efficacy of 95%, the risk referred to above is 4% if the sample size is 100, 1% for 125, 0.5%, for 150, and 0.1% for 200. What constitutes an 'acceptable risk' must be determined by the investigator, but for three values (1%, 5%

and 10%), the resultant recommended sample sizes are set out in Table 3. If 95% efficacy is regarded as sufficiently effective, the sample size must be 154 for <1% misclassification risk, 112 for <5% risk, and 93 for <10% risk. The corresponding figures for 90% efficacy are 216, 155 and 127, respectively. These

TABLE 2

Risk of classifying Insufficiently effective regimen fit sufficiently effective regimen

Definition of "Sufficiently effective" regimen*(%)	Definition of "Insufficiently effective" Regimen*(%)	Risk (%) of classifying insufficiently effective regimen as, sufficiently effective with the following sample size								
		100	125	150	375	200	225	250	275	300
99	89	0.1	0	0	0	0	0	0	0	0
95	88	0.5	0.1	0	0	0	0	0	0	0
97	87	1	0.3	0.1	0	0	0	0	0	0
96	86	2	0.8	0.2	0.1	0	0	0	0	0
95	85	4	1	0.5	0.2	0.1	0	0	0	0
94	84	5	2	0.9	0.4	0.1	0	0	0	0
93	83	7	3	1	0.6	0.2	0.1	0	0	0
92	82	8	4	2	0.9	0.4	0.2	0.1	0	0
91	81	10	5	3	1	0.6	0.3	0.1	0.1	0
90	80	12	6	3	2	0.9	0.4	0.2	0.1	0
89	79	13	7	4	2	1	0.6	0.3	0.2	0.1
88	78	15	9	5	3	2	0.8	0.5	0.2	0.1
87	77	16	10	6	3	2	1	0.6	0.3	0.2
86	76	18	11	7	4	2	1	0.5	0.4	0.2
85	75	19	12	8	5	3	2	1.0	0.6	0.3
84	74	20	13	8	5	3	2	1	0.7	0.4
83	73	22	14	9	6	4	2	1	0.9	0.5
82	72	23	15	10	6	4	3	2	1	0.6
81	71	24	16	11	7	5	3	2	1	0.8
80	70	25	17	12	8	5	3	2	1	0.9

*in terms of therapeutic efficacy in those who complete the prescribed course of chemotherapy.

TABLE 3

Recommended sample sizes for determining whether or not a regimen is sufficiently effective

Definition of "Sufficiently effective" regimen*(%)	Definition of "Insufficiently effective" regimen*(%)	No. of patients in analysis			No. of patients to be admitted@		
		Misclassification risk** of			Misclassification risk** of		
		<1%	<5%	<10%	<1%	<5%	<10%
99	89	94	71	61	118	89	76
98	88	110	82	69	138	102	86
97	87	126	93	78	358	116	98
96	86	140	102	85	175	128	106
95	85	154	112	93	192	140	116
94	84	167	121	100	209	151	125
93	83	180	130	107	225	162	134
92	82	193	139	114	241	174	142
91	81	205	147	120	256	184	150
90	80	216	155	127	270	194	159
89	79	228	163	133	285	204	166
88	78	239	170	139	299	212	174
87	77	249	177	144	311	221	180
86	76	259	184	150	324	230	188
85	75	269	191	155	336	239	194
84	74	279	198	160	349	248	200
83	73	288	204	165	360	255	206
82	72	297	210	170	371	262	212
81	71	305	216	175	381	270	219
80	70	313	221	179	391	276	224

*in terms of therapeutic efficacy in those who completed the prescribed course of chemotherapy.

**i.e. risk of classifying insufficiently effective regimen as 'sufficiently effective'.

@assuming a 20% drop-out rate over a 2-year period.

findings suggest that, if 90-95% is regarded as sufficiently highly effective, the minimum sample size for analysis must be 90 to 130. Table 3 also sets out the recommended intake to study, assuming a 20% drop-out rate over a 2-year period. The findings suggest that the minimum intake should be of the order of 120 to 160.

Discussion

A feature of most clinical trials of short-course regimens is that one is operating with regimens that are usually of high efficacy and are not appreciably different from one another. Consequently, the sample size needed for demonstrating significant differences between regimens tends to be very high. Our computations indicate that differences of less than 10% are often likely to be missed, and that even a difference of 10% can be detected only if the number of patients evaluated is of the order of 150-200 per treatment group.

We examined 25 reports on short-course regimens published during the period 1974-85 in the American Review of Respiratory Disease, Tubercle, Indian Journal of Tuberculosis, Lancet, Chest, and Lung India. Of these, 21 dealt with comparisons, involving a total of 81 regimens. Their distribution according to the number of patients employed in evaluation, and the country of study, is set out in Table 4. Of the 81 regimens, only 33 (41%) had a sample size of 150 or more; further, as many as 32 (40%) had a size of less than 100, including 5 (6%) with less than 50 patients. There was considerable difference with respect to sample size between studies undertaken in India and those undertaken elsewhere. Thus, none of the 17 regimens in India had a size of more than 150 as compared to 52% of 64 undertaken elsewhere ($P < 0.001$). At the other extreme, 82% of the former had less than 100 patients each as compared to 28% of the latter ($P < 0.001$).

TABLE 4

Distribution of short-course regimens according to number of patients employed for evaluation

Number of patients used For evaluating the regimen	All countries		India		Other countries		
	No. of regimens	%	No. of regimens	%	No. of regimens	%	
Less than 25	1 } 4 }	6	1 } 3 }	24	0 } 1 }	2	
50 -74	12 } 15 }	33	8 } 2 }	59	4 } 13 }	27	
75- 99							
100—124	9 } 7 }	20	0 } 3 }	18	9 } 4 }	20	
125-. 149							
150—174	7 } 17 }	30	0 } 0 }	0	7 } 17 }	38	
175—199							
200—224 225- 249 250 or more	9 } 0 } 0 }	11	0 } 0 } 0 }	0	9 } 0 } 0 }	14	
Total	81	100	17	101	64	101	

The implications of the inadequacy of numbers are that the investigators could have wrongly concluded in some of these trials that regimens had similar efficacy when indeed they were appreciably different. The long-term consequences of such an error could be serious, especially if it has a bearing on the choice of regimens for mass treatment programmes. Consequently, the temptation to undertake studies on short series of patients needs to be firmly resisted. An additional bias associated with small studies is that it is likely that only those with optimistic conclusions (i.e. no significant difference, highly effective combination) are submitted for publication.

With the alternative approach described, wherein one is testing for whether a regimen is sufficiently highly effective for recommending

its use in a tuberculosis programme, about 100-125 patients *in the analysis* would be adequate, as compared to 150-200 for demonstrating significant differences between two regimens. In general, the sample size will be smaller with the alternative approach. This suggests that it would, be valuable to determine, even at the planning stage, which of the two approaches is more relevant to the clinical trial under consideration.

Fox, W. and Mitchisyn, D.A. : Suit.; of Art-Short-course chemotherapy for Pulmonary Tuberculosis: **Amer. Rev. Resp. Dis.**, 1975, **111**, 325.

Walters, D.E. : In defence of the Arc sine approximation; **Statistician**; 1979, **28**, 219.

SURGERY IN RESPIRATORY DISEASES*

BY S.B. TRIVEDI**

At the outset, let me mention that I am extremely thankful to the Incentive Committee of the Tuberculosis Association of India, for selecting me for the Wander-TAF Oration of the year 1985. I feel highly delighted by the honour bestowed on me- particularly when I remember the names of the stalwarts in the field who have delivered these orations in the past, I would also like to express deep sense of gratitude to the house of Wanders for their support to the cause of the fight against Tuberculosis for last many many years. When selected for this oration, as a Surgeon, my obvious choice for the subject, was Surgery in Respiratory Diseases and, while speaking on this subject, I remember, with deep regard, the names of the surgeons who used to be with us in these Conferences in the past, viz. Dr. Reeve H. Belts, my respected teacher with whom I was at Vellore for 2 years. Colond Chuck, Or. Thomson Wells, and Dr. Dingle)', whom we lost only very recently. Without them, I feel very lonely, amongst the Chest Physicians and I therefore shall try to highlight the fact. In this oration, that more and more Chest Surgeons should get involved and assist in the management of the Respiratory Diseases

History : The time at my disposal, and the vastness of my subject will not permit me to go into the historical details of the early stages of the development and progress of Chest Surgery which, of course, is a story of human courage and boldness. I must however mention the fact. In the early days, surgical methods were used for the management of Pulmonary TB and cases of lung abscesses even before the advent of antibiotics and chemotherapy. We are all aware of the collapse procedures practised in '30s' and '40s' like Artificial Pneumothorax, Pneumopertoneum, Phrenic crush, conventional and. Plombage plastics. Even Resections were attempted in early days, very often with disastrous results. However, with the advent of specific chemotherapy and improved technique of anaesthesia, which gave the facilities of positive pressure breathing, controlled respiration with relaxants and even one lung anaesthesia, with bronchial blockers, the intra-thoracic surgical procedures, became relatively safe and resectional surgery of lung was increasingly done. Contribution of surgical assistance to the management of lung diseases has shown periods of

waxing and waning. In the early days, surgery was resorted to more out of desperation, because we had no antibiotics and chemotherapy. Use of surgery became a little less frequent, when the antibiotics and chemotherapy became available. However, with improved techniques of anaesthesia and surgery. Resections were resorted to more frequently and more safely; 1945 to 1965 were the years when surgical assistance for the management of TB and other lung diseases was maximum, in the form of Resectional Surgery, under cover of good chemotherapy, and the results were excellent. In the years after 1970. with the massive drive for early case detection and the use of newer and more effective anti-tuberculous chemotherapy, the need for surgical intervention declined. However, surgical procedures, even today when rightly indicated, and when performed in time are a big assistance to drug therapy for the control and cure of respiratory diseases.

The material for today's presentation has been drawn entirely from the cases that came to us at the Amargadh Chest Hospital during last 25 years. Amargadh Institute was started as a small 48 bedded TB Sanatorium, in rural Saurashtra in 1949, but has now become a 750 bedded, full-fledged well equipped chest hospital. The material presented deals with the type of cases usually encountered, in the routine hospital practice, in a developing country like ours. Highly theoretical and academic considerations are intentionally omitted.

For the sake of ease and simplicity of presentation. I have decided to consider the use of Surgery in Respiratory diseases in three distinct groups :

(1) *Surgery in Acute Respiratory distress*

These are the type of cases where usually surgical intervention is not only absolutely essential but is an emergency. Surgical relief must be provided in these cases, as rapidly as possible, as otherwise the life is in danger.

(2) *Surgery In Pulmonary Tuberculosis*

This is for a group of cases, where there are definite indications for surgery, and if done in time, in rightly indicated cases, it can be of great

*Wander-TAF Oration (1985).

**Medical Superintendent K.J. Mehta TB Hospital & TB Research Centre, Amargadh,

assistance in curing the patient, and also in controlling the spread of the disease. In a developing country like ours, where the cases cannot still be diagnosed early enough and where effective chemotherapy for the desired duration is not always possible, because of socio-economic and other reasons, we do come across cases where surgery will help in the control and cure. In such cases, the only plea is that the surgical intervention should not be delayed, because if delayed, it may not be possible at all.

(3) *Surgery in non-tuberculous lung diseases*

Lung surgery is being performed with greater frequency now for this group. In developed countries particularly, where incidence of pulmonary tuberculosis has gone down, these conditions have now been, the main indications for lung-resectional surgery and that too with increasing frequency. The main indication is pulmonary neoplasms.

I Acute Respiratory Distress

These conditions as indicated require immediate surgical intervention as a life-saving procedure. These conditions are commonly seen in infants and children, but are also seen quite often in adults. These conditions can be grouped as follows:

Acute dyspnoea caused by intraluminal airway obstruction is seen most commonly in children, and the commonest causes for this obstruction are either (i) laryngeal edema or (ii) a foreign body in the air passage.

Acute laryngeal edema may be diphtheritic in origin or may be due to allergic angioneurotic edema. The child usually comes in a gasping state with severe indrawing of the ribs. The clinical picture is usually very typical and almost diagnostic. An immediate tracheostomy relieves the dyspnoea completely and subsequent treatment with antibiotics and corticosteroids removes the laryngeal edema and the tube can be removed after about a week.

In cases of obstruction due to inhalation of a foreign body, again the signs are fairly typical. The foreign body may be radio-opaque when it is localised easily on an X-ray or it may be a vegetative foreign body like a tamarind seed or a groundnut. Diminished air entry on one side is fairly diagnostic and an immediate bronchoscopic removal of the foreign body completely relieves the distress. In some infants under the age of 2 years, we have found that the removal of the foreign body by bronchoscopy through a tracheostomy is far easier and safer

and hence we have almost made it a routine practice to remove the foreign body in infants by bronchoscopy through a tracheostomy.

(2) A massive pleural collection on one side causes acute respiratory distress. The cause may be tuberculous or otherwise, but an immediate drainage by an intercostal catheter connected to an underwater seal drainage gives complete dramatic relief.

(3) Similarly, a large sudden massive pneumothorax gives an acute respiratory distress. In children, this occurs quite often after an attack of measles while in adults with emphysematous chest, this can occur due to rupture of a bulla. Here also, an immediate intercostal drainage gives total and complete relief,

(4) Accidental or intentional trauma to the chest is another cause of acute respiratory distress.

A deep penetrating stab wound requires a thorough exploration by thoracotomy and subsequent closure after putting in a drainage tube. Closed thoracic trauma resulting in fracture of the ribs is quite often very deceptive. Simple fracture of the ribs, or double fracture with a flail chest can give severe dyspnoea but is often relieved by strapping. But often a closed trauma with fracture of the ribs can produce a large pneumothorax or a hemo-pneumothorax and this again requires an immediate intercostal drainage for total relief.

II. Surgery in Pulmonary Tuberculosis

Casts of pulmonary Tuberculosis form another large group where, in some cases, surgical intervention and assistance, if offered in time, can be a big help in complete cure of the disease. There is an increasing belief among the phthisiologists that with the advent of drugs like Rifampicin and Pyrazinamide, there is hardly any need for surgery in Pulmonary Tuberculosis. This is unfortunately not true, particularly for a developing country like ours where the diagnosis and detection of cases is not done early enough. And when these cases are detected late, the disease has already done such a lot of damage to the parenchymal tissue and the bronchial tree that, at least in some of them, surgery is needed for complete cure, and to make the patient completely asymptomatic.

There are very definite and simple indications for surgical intervention and these are as follows:

- (1) *A destroyed lung* ∴ If the opposite lung is reasonably healthy, **pneumonectomy** is, advisable for a destroyed Tuberc

lous lung that has multiple cavities and a lot of disease in the bronchial tree with bronchiectatic changes or bronchostenosis. because even after sputum conversion, the patient remains badly symptomatic. He brings out a lot of sputum, often has pyrexia and toxemia due to secondary infection, and can even have repeated haemoptysis. Removal of this destroyed lung makes him completely asymptomatic.

- (2) *Destroyed lobe* : Just like a destroyed lung, a damaged, destroyed lobe can be a potential source of morbidity and it is good to do a lobectomy and remove the lobe.
- (3) *A failed thoracoplasty*: Quite often when full facilities are not available, a thoracoplasty is done for a localised persistent apical cavity. Sometimes the cavity does not close well, and after a few years the disease shows reactivation with positive sputum. For such cases, a total lung resection can be and should be done, under the thoracoplasty.
- (4) *Failed chemotherapy* : Occasionally, we do come across some cases where the patient has meticulously taken the recommended specific effective chemotherapy for sufficient length of time and even then he remains sputum positive, toxic and symptomatic. In such cases, though they are to be considered as bad surgical risk patients, a lung resection must be done.
- (5) Lastly, surgery is indicated in some of the complications of pulmonary TB and the most important of these is empyema. Treatment of tuberculous empyema has to start with plain and simple intercostal drainage. This relieves the patient of pyrexia and toxemia. Most often with persistent drainage and continuous negative suction pump, the lung re-expands completely and the tube can be removed. But in some cases the underlying lung is so badly shrunken and fibrosed that it cannot come out. Under such circumstances, the empyema space can be closed totally by a total 9-rib plasty. Attempted decortication in such cases most often fails, as even after the decortication, the fibrosed lung does not expand, the space persists and thoracoplasty becomes necessary to achieve space obliteration. More radical and drastic operation of pleuropneumonectomy also can be done, but like decortication, pleuro-

pneumonectomy also is not very successful because most of the time we end up with a bronchopleural fistula, a dreaded complication of resection. And, subsequently, for this again a total thoracoplasty is needed. For a tuberculous empyema, therefore a simple intercostal drainage is enough to bring the lung out, but if this does not succeed, the best alternative is a total space obliterating thoracoplasty.

Another complication for which a resection is sometimes indicated is recurrent haemoptysis. The case is which a localised solitary cavity is responsible for recurrent haemoptysis, a lobectomy or a pneumonectomy is the best choice.

III. Surgery in non-tuberculous lung diseases

The final group is that of non-tuberculous lung diseases. Amongst these, following are the conditions where surgery is indicated:

- (1) Total cystic disease of the lung, if unilateral, is best treated by a pneumonectomy.
- (2) A large thick-walled chronic lung abscess should better be treated by a lobectomy.
- (3) Localised bronchiectatic changes in a lobe or segment, particularly in a young patient, should better be removed by a segmental resection or a lobectomy. Even bilateral segmental resections have been done for localised bronchiectasis with great success.
- (4) Presence of a large hydatid cyst in the lung indicates removal of the cyst, which is a relatively simple and uneventful procedure.
- (5) Huge air cyst or an emphysematous bulla, that makes the patient dyspnoeic on slightest exertion and a respiratory cripple, can be removed surgically with good relief. The total cyst wall is excised, and the bronchial opening is closed. The remaining lung then re-expands to fill up the space, with improved ventilatory capacity.
- (6) Early suspected pulmonary neoplasms in the form of small rounded opacities, should better be removed early, as delay may make the growth inoperable.
- (7) There are some cases, where there is an opacity of uncertain aetiology. Quite

often, these cases are put on anti-tuberculous treatment straight away, but even after regular and prolonged treatment, if there is no change in the opacity, an exploratory thoracotomy is indicated, and the lobe or the lung should be resected.

In conclusion, one can say;

(1) Surgery has a definite place in the ma-

nagement of some of the respiratory diseases.

(2) There are definite indications where and when surgical intervention will accelerate and help the complete cure of the disease,

(3) If indicated, surgical help should not be delayed.

NEW AWARDS FOR OUTSTANDING RESEARCH

The recently established Ranbaxy Research Foundation has announced two annual awards of Rs. 50,000'-each for outstanding research work in medical and pharmaceutical sciences.

Indian nationals resident in India or abroad, who have not already received a major award for a particular research work will be eligible for sponsorship by heads of institutions such as universities, medical and pharmacy colleges, civil and military health services, and state level education and research centres, among others. The nominations would be received by the Foundation at 19, Nehru Place, New Delhi-19, till 31st May, 1986.

Excerpts from the Presidential Address of Dr. D. Umapathy Rao

- (1) Priority should be given to detecting sputum positive cases among the chest symptomatics attending the various health institutions in the country.
- (2) Regular and continuous supply of drugs and X-ray films is essential.
- (3) Improvement in the method of drug distribution, surveillance, detection and retrieval of drug default are essential for improving the patients' compliance in domiciliary treatment.
- (4) National Tuberculosis Programme should be a 100% centrally sponsored scheme, at least during the 7th, 8th and 9th Five Year Plans, so that the financial constraints of States may not hamper the implementation of all the provisions of the National Tuberculosis Programme.
- (5) General Practitioners who are willing to follow the requirements of the National Tuberculosis Programme and maintain minimum records should be supplied drugs by the government for free distribution to their bona fide tuberculous patients.
- (6) Facilities available at the Tuberculosis Demonstration and Training Centres should be utilised for training of personnel and operational research studies.
- (7) The tempo of Tuberculosis Programme should be further intensified.

Summaries of Papers presented at the 40th National Conference on Tuberculosis & Chest Diseases at Shillong from 16th to 18th November, 1985

LUNG DISEASE IN BHOPAL GAS VICTIMS

S.K. JAIN AND N.P. MISRA

1. A single inhalation of the toxic gas caused acute lung injury and severe respiratory disease with a high rate of mortality.
2. In the survivors, the pathological changes resolved to a variable extent leaving a large number of patients with residual lung lesions.
3. The disease is characterised predominantly by obstructive lesions in the airways—especially the smaller bronchioles—with intra and peri-bronchial cellular infiltration, oedema and fibrosis.
4. Additionally, there is alveolar obliteration, cellular infiltration and fibrosis—patchy in distribution in most but may be diffuse in others.
5. Clinically, major symptoms comprise breathlessness on exertion, cough with or without expectoration, reduced work capacity and chest pain—with rales and rhonchi in nearly 50% of them.
6. Lung function testing shows evidence of airflow limitation, alveolar hyperinflation and air trapping; impairment of diffusion in only a few but a normal KCO in all, slight hypoxaemia in nearly 50% but no CO₂ retention.
7. Exercise capacity is limited by dyspnoea and or muscle fatigue often without the patient reaching maximum ventilation or cardiac responses. The explanations are not clear.
8. Clinical and radiological features are poorly correlated with lung function and exercise test data.

CHANGES IN PULMONARY FUNCTION IN VICTIMS OF BHOPAL TRAGEDY

V.K. VIJAYAN *et al*

Clinical, pulmonary function and blood gas studies carried out in symptomatic Methyl Isocyanate exposed individuals 1-2 months after exposure had revealed that 40% of them had ventilatory impairment. The predominant type of ventilatory defect was combined obstruction and restriction. Five percent of patients with normal physical findings and normal chest X-rays had abnormal pulmonary function. Arterial hypoxia (PaO₂ < 85 mm Hg) was observed in 69% of patients in whom blood gas analyses were done. Arterial hypoxia and ventilatory abnormalities were predominantly seen in severely exposed patients. Further studies are required to identify the sub-group of patients with Reactive Airways Dysfunction Syndrome. Long term follow up is essential to identify the pulmonary syndromes due to MIC exposure.

CERVICAL LYMPHADENOPATHY—CLINIC O-PATHOLOGICAL CORRELATION

K.C. MOHANTY

Fifty seven cases of cervical lymphadenopathy were subjected to biopsy. Histopathological and bacteriological examinations for AFB by smear and culture were carried out. Histopathological evidence of tuberculosis was obtained in 48 of the patients. Bacteriological confirmation could be obtained only in 14 of these.

TUBERCULOMA- BRAIN

P.K. BAM

Five cases of tuberculous of the brain were detected during the last one year in the Centenary Hospital, Calcutta Port Trust. Three of them were under the age of 20 years. The location of tuberculoma was subtenorial in one and supratentorial in the other 4, None had a BCG scar. Three patients had tuberculous meningitis simultaneously. C.T. Scans have revolutionised the diagnosis of tuberculoma.

EXTRA-PULMONARY MANIFESTATION AS OBSERVED IN CASES OF PULMONARY TUBERCULOSIS—A REVIEW OF 1,000 CASES

B.N. PANDA, *et al*

Out of one thousand consecutive male patients of pulmonary tuberculosis in the age group 18-54 years treated in the Armed Forces Hospital, Pune, during 1983-85, thirty three had associated extra pulmonary involvement. Fifty eight percent of this latter group were sputum negative by smear and culture as against 32 per cent in the entire group. The sites of involvement were pleura (12), gastrointestinal tract (6), lymphnodes (4), osteoarticular system (4), genito-urinary organs (3), central nervous system (2), eye (2), skin (1) and pericardium (1). One patient had multiple organ involvement. Patients with associated extra pulmonary lesions had less extensive and predominantly non-cavitary disease. From this study it appears that in cases of pulmonary tuberculosis, chances of having extra-pulmonary involvement is 3 times more in patients whose sputum is negative for mycobacterium TB by smear/culture than in the sputum positive cases.

CHEMOTHERAPY STUDIES IN TUBERCULOUS MENINGITIS IN CHILDREN

PADMA RAMACHANDRAN

(Paper being published in full)

CHOICE OF SAMPLE SIZE IN SHORT-COURSE CHEMOTHERAPY TRIALS

M.C. SATAGOPAN (Paper

being published in full)

APPLICATION OF SHORT-COURSE CHEMOTHERAPY UNDER FIELD CONDITIONS

M.L. MEHROTRA

Results of 248 bacteriologically confirmed urban and rural cases of pulmonary tuberculosis were analysed. The duration of treatment was 32 weeks and the regimens were 4 RHZS/16 R₂H₄Z₂/12 R₂H₂ and 4 R₃H₂Z₂S₂/8 R₂H₂Z₂/20 R₂H₂. Drug compliance was about 69% in both regimens. In the first regimen, all patients had favourable results and the relapse rate was 7% in the first year of follow-up. In the second regimen, the results of treatment were favourable in 93 % of whom 21 % relapsed during the first year. Amongst those who had had earlier treatment, immediate favourable results were 91 % and the relapse rate among them was 37%. The adverse effects of the drugs were noticed in 15% and 6% respectively while treatment had to be discontinued in 5% and 1,4% respectively in the two regimens.

CLINICO-RADIOLOGICAL SEQUELAE IN TREATED CASES OF PULMONARY TUBERCULOSIS

V.P. GOPINATHAN. *et al*

Clinico-radiological sequelae in 175 adult males suffering from pulmonary tuberculosis were analysed one year after completion of chemotherapy. The diagnosis was bacteriologically confirmed in 70% of the patients. Twenty six percent continued to have residual symptoms without any activity of the tuberculous lesion. Seventy eight percent had residual radiological opacities. Ten patients showed evidence of reactivation of disease needing re-treatment during the period of follow-up. Sequelae were observed very often in patients with far advanced smear positive initial disease and in those who had incomplete chemotherapy.

ETHAMBUTOL AND OPTIC NEURITIS WITH SPECIAL REFERENCE TO SERUM ZINC AND COPPER

P.R. GUPTA, *et al*

One hundred and four previously untreated bacteriologically confirmed cases of pulmonary tuberculosis were studied. Thirty five were not given any Ethambutol. Thirty four were given Ethambutol 25 mg/kg per day and 35 were given 35 mg/kg. Eighteen healthy subjects served as controls. None, 1 and 4 patients respectively in the three treatment groups had complaints suggestive of optic neuritis which was confirmed objectively only in 3 out of the 4 patients in high-dose Ethambutol group. Decline in serum zinc levels was noticed in both the Ethambutol groups, but the decline was significant only in the higher dose Ethambutol group. Serum copper levels were unaffected. All patients developing optic neuritis were males, under 30 years of age and moderately to severely under-nourished.

ERRORS OF PRESCRIBING ANTI-TB DRUGS—A MEDICAL AUDIT

B.L. JETHWANI

Three thousand prescriptions of previous treatment by 1,602 patients admitted in a sanatorium were reviewed. Nearly 82% of the prescriptions included three or more anti-TB drugs, 6% had only one drug and 3% had 5 to 6 anti-TB drugs. INH, Ethambutol and Rifampicin were the commonest drugs (70-75%). Streptomycin was included in nearly 1/3rd of the prescriptions and Pyrazinamide in about 1/5th of the prescriptions. In 19% of the prescriptions, dosage was wrong and in 13% the frequency of drug administration was faulty. Percentage of wrong prescriptions was 1.5%, 22.6% and 33.3% among tuberculosis specialists, other qualified physicians and unqualified physicians, respectively. The prescription was wrong in the case of 4% of the patients who had previously had treatment in a tuberculosis hospital.

SUPPURATIVE LUNG DISEASE—STUDY OF 39 CASES

G.S. PERHAR

A retrospective analysis of 39 patients with suppurative lung diseases was carried out. Males predominated and the maximum number of cases were in the age group 31 to 40 years. Staphylococcus aureus coagulase positive was the commonest causative organism which was resistant to most of the routinely used antibiotics, followed by Klebsiella pneumonia. Bronchoscopy was non-contributory in 1/3rd of the cases. Only three patients required surgical treatment. Chemotherapy alone was enough in all other cases. In one case, left parietal lobe abscess was seen as a metastatic complication.

OVARIAN FUNCTION AFTER EFFECTIVE TREATMENT OF PULMONARY TUBERCULOSIS

(MRS.) S.N. TRIPATHY

The study was based on a prospective study of 50 consecutive bacillary cases of pulmonary tuberculosis hospitalised during one year (1983-84). Gynaecological investigations could be completed after treatment of pulmonary tuberculosis in 35 patients. Fourteen of these received conventional chemotherapy and the other 21 short-course chemotherapy. None of the 35 cases

showed a relapse in 6-12 months' period of follow-up. In nearly 3/4th of the cases ovarian function returned to normal after treatment and nearly 1/3rd of these became pregnant also. It is not clear whether irreversibility of the ovarian function in some cases was due to complete destruction of the ovary and/or endometrium or the prolonged course of pulmonary tuberculosis affected the ovarian function in some other way.

ELECTROCARDIOGRAPHS ABNORMALITIES IN UNTREATED CASES OF PULMONARY TUBERCULOSIS

S.N. TRIPATHY, *Et al.*

The study is based on 64 patients of bacteriologically confirmed cases of pulmonary tuberculosis. Males and females were approximately equal and majority of them were in the age group 30-39 years. Majority of the cases had severe degree constitutional disturbances. ECG abnormalities were seen in 30 cases and almost all of them had far advanced pulmonary disease. The various types of ECG abnormalities seen in these cases were analysed.

PANEL DISCUSSION ON "MODALITIES OF CASE-HOLDING"

MODERATOR : DR. P.A. DTSHEKUMH *Panelists : I,*

Ranga Rao, S.K. Khasgiwala and M.A.Seetha

Case-holding, which along with case-finding, is essential for tuberculosis control, was defined as the process of ensuring that the patient adheres to the prescribed treatment regimen for the prescribed period of treatment. Case-holding was reported to be about 30% in an average DTP. In better served urban areas, 70-80% of the patients completed the duration of treatment. The problem is of great magnitude, in general.

The pre-requisites of case-holding were identified as operational (pertaining to distance between the drug distribution centre and the patient's residence, working hours of the treatment centre and regularity of drug supplies); organisational (importance of proper address of the patient, efficiency of defaulter retrieval system and availability of health facilities for this purpose) and technical (nature of treatment and regimen). The pros and cons of bi-weekly intermittent regimens were discussed in detail. Symptomatic relief and false sense of cure arising from that was considered to be the most common cause of drug default. The importance of motivation to avoid default and the role of doctors, multi-purpose workers, village health volunteers and voluntary organisations was stressed.

FATE OF TREATMENT DEFAULTERS : A BACTERIOLOGICAL ASSESSMENT

K. JAGANNATH, *et al.*

Results of 60 previously untreated patients who were on short-course chemotherapy and 66 re-treatment cases who were on a bi-weekly regimen were analysed. Twenty three untreated and 15 re-treatment cases were positive by smear and culture; 1 and 3, respectively, were smear negative but culture positive; 36 and 48, respectively, were smear negative and culture negative. The bacilli were found to be sensitive to all drugs in all culture positive cases. Sputum continued to be positive or there was a reversion to positivity after initial concession more frequently in patients who had extensive or moderately advanced pulmonary lesions. Case retrieval procedures should be intensive to keep these persons regular. Similarly, concerted efforts are necessary to retrieve early treatment defaulters. Sputum conversion was less in defaulters who had irregular treatment before default.

FATE OF RURAL LOST CASES IN A DISTRICT TB PROGRAMME

B.S. NAGARAJA RAO, *Et al*

Out of the 370 patients treated during 1982-84 who were eligible for the study, 60 cases could not be traced for want of adequate address or due to migration. Out of the 310 cases who had stopped treatment prematurely and could be traced, 10% had died, 10% were treatment failures and 80% had been cured. Some of the cases who had dropped out of the treatment earlier resumed treatment sometime later.

PROBLEM OF DEFAULT AND FATE OF DEFAULTERS

M.A. RAHIM AND R. PATHASARATHY

The study was carried out at DTC, Thanjavur during 1983-84 with the object of determining the quantum of default with reasons thereof and to determine the fate of defaulters in relation to their bacteriological and radiological status both at the start of treatment and at the time of default. There were 3,291 defaulters out of which 2,337 were attending the DTC and 954 were taking treatment in the various PHIs. The average number of defaults per patient was 5.6 in the PHIs and 3.7 in the DTC patients. Seventy five percent of the defaulters had 50% or more of drug collection as against 43%, amongst the PHIs defaulters. Sixty eight percent of the defaulters could be retrieved.

RETROSPECTIVE STUDY OF 245 DEFAULTERS REPORTING BACK TO DTC ON THEIR OWN

R.A. SHARMA

Two hundred and forty five patients had stopped taking drugs after varying periods of treatment between July 1982 and December, 1984. The commonest cause of default was relief of symptoms followed by migration. Reappearance of symptoms was responsible for their reporting back at the DTC after earlier default. Some patients defaulted because of pregnancy and some because injections were not given to them (which they thought was essential for treatment). Bacteriological status at the time of reporting back after default depended upon the duration of treatment which the patient had before default and the interval between default and reporting back.

ROLE OF REPEAT SPUTUM MICROSCOPY IN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS

M. SUNDARAMMA. *Et. Al.*

The study is based on 4,063 patients who were considered to be suffering from pulmonary tuberculosis on the basis of clinical and radiological evidence. Of these, 1,619 were positive for AFB by microscopy of the spot specimen of sputum. Of the 2,444 whose spot specimen was negative, 1,672 were included in the study, for which first specimen of sputum brought out by the patient immediately after waking up in the morning was examined. Four hundred and eighty eight were positive on the first day, 2 on the second day and 5 on the third day.

DISTRICT TUBERCULOSIS PROGRAMME : MATERIAL AND METHODS FOR ENHANCING CASE-FINDING AND TREATMENT ACTIVITY IN RURAL AREAS : AN OPERATIONAL ASPECT

R.C. SHARMA, *et al*

Case-finding camps were organised in the rural areas of the district with a view to improve case-finding. The Camps were preceded by an intensive publicity campaign. Before the Camp, sputum of 478 symptomatics was examined and 5 were found to be positive. As a result of the Camps, 7,335 symptomatics were examined and 730 fresh sputum positive cases were identified. Of the 730 freshly discovered cases, 360 were initial defaulters but 110 of these could be called subsequently for starting treatment.

ROLE OF PARA-MEDICAL PERSONNEL IN NATIONAL TUBERCULOSIS PROGRAMME

J.L. MONGA

The role of para-medical workers should consist of identifying the chest symptomatics, collecting proper specimens of sputum from them and arranging for examination of the sputum. In respect of case-holding, their most important function is to motivate the patient and the family for regular treatment. Treatment regimens must be acceptable to obtain better compliance from the patients and the para-medicals must identify adverse reactions as early as possible. Health education with a view to create public awareness, to maintain proper record of treatment with a view to detect drug default, as early as possible, and to take prompt defaulter action are the other

responsibilities of a para-medical worker. The need for improved working conditions and better emoluments for the para-medical workers was stressed.

A COMPARATIVE ASSESSMENT OF THREE MOTIVATION PROCEDURES FOR SUCCESSFUL COMPLETION OF TREATMENT—INTERIM RESULTS

(New Delhi Tuberculosis Centre)

Three different procedures of motivation of domiciliary patients of pulmonary tuberculosis in respect of regular drug taking were compared. In all three procedures, initial motivation was provided at the centre. However, recurrent motivation at 4 weekly intervals was provided according to three different procedures:-

- A. Motivated at *Centre* by *Health Visitor*
- B. Motivated at *Home* in presence of at least 2 adult family members by *Health Visitor*
- C. Motivated at *Centre* by *Doctor*.

The same drug regimen (8 HR7F/24 TH) was prescribed to all patients, the total treatment lasting 32 weeks.

An interim analysis covering the first 16 weeks of treatment of 65 patients showed that during this initial period there was not much to choose between the three procedures. However, substantial differences were noted when data covering the first 24 weeks were analysed for the 35 patients who had completed this period. In Procedure A the average number of drug days lost was 16.3 and in B 3.2. days. In procedure C, where the medical officer provided the motivation, the average was the highest i.e. 22.3 days. From this limited analysis it appears that procedure B has an edge over others but final conclusions must await completion of the study.

A STUDY OF PHARMACOKINETICS OF PYRAZINAMIDE IN TUBERCULOSIS PATIENTS

MRS. SANDHYA KULSHRESTHA

(Paper being published in full)

ALLERGEN TESTING AND HYPOSENSITISATION

P.A. DESHMUKH, *et al.*

Two hundred and fifty eight cases consisting of bronchial asthma (112) allergic rhinitis (72) and both together (74) were studied. One hundred and forty four of the patients were males and nearly 3/4th of the patients were in the age group 15-44 years. House dust was found to be the most frequent allergen followed by Candida, rice grain dust and 11 varieties of pollen. Hyposensitisation with specific vaccine was possible in 50 cases. Of these, 14% showed good improvement, 36% moderate improvement and 12% mild improvement. In 38%, hyposensitisation was a failure. Improvement was obtained within 16 weeks. Patients with definite history of periodic or seasonal exacerbations are likely to be benefitted. Multi-reactors do not benefit and patients in the younger age group fare better.

A STUDY OF INTRADERMAL ALLERGY TESTING IN BRONCHIAL ASTHMA IN RAIPUR

B. SARKAR, *et al.*

Intra-dermal testing was carried out in 50 patients of bronchial asthma and compared with 10 healthy controls. Thirty five of the patients were males, 86% had allergic rhinitis, 22% urticaria, 20% food allergy and 8% had associated eczema. Extrinsic asthma was more frequent than intrinsic. Seventy four allergens were used for skin testing. Dust and insects were the two most frequent offending allergens.

SKIN SENSITISING TEST AND TOTAL SERUM IgE LEVELS IN NORMAL AND VARIOUS ALLERGIC DISORDERS

S.K. SAHA, *et al.*

The study is based on 40 patients. Total mean serum IgE in healthy individuals was found

to be 41 ± 29 KU/L and the upper limit of normal values was found to be 105 KU/L. In allergic patients, serum IgE was found to be 502 ± 376 K.U/L... Asthmatic patients had higher mean levels than those suffering from either seasonal Rhinitis or Conjunctivitis., Exceptionally high levels strongly raised the suspicion of parasitic infestation,

LONG-ACTING TRIAMCINOLONE ACETONIDE IN CASES OF BRONCHIAL ASTHMA

BALDEV RAJ, et al.

Sixty patients of chronic bronchial asthma were studied. Twenty patients were given salbutamol daily. 20 patients were put on Triamcinolone Acetonide, (TA) once a month and 20 patients were put on TA once a month as well as salbutamol daily. The response was fair in 12, poor in 5 and worse in 3 patients in salbutamol group. excellent in 15 and good in 5 in TA group and excellent in 17, good in 1 and poor in 2 in the group which was given both the drugs. TA provides rapid relief of symptoms and longer periods of remission as compared to salbutamol.

IMMUNOTHERAPY IN MANAGEMENT OF ALLERGIC BRONCHIAL ASTHMA

M.A. AGNIHOTRI, et al

Out of 1055 patients who attended the Allergy Clinic between May 1982 and August, 1984, nearly 69% suffered from respiratory allergic diseases. Twenty eight percent had skin allergy and 3% had drug allergy. Amongst the respiratory patients, nearly 90% suffered from bronchial asthma with or without other allergic manifestations and nearly 10% had only rhinitis. Immune-therapy was given to 468 patients out of 500 with allergic bronchial asthma. The remaining 32 patients were excluded because the identity of the offending allergen could not be established. Of the patients who took treatment regularly for 12 months, nearly 88% showed improvement, The improvement rate went up to 96% in those who took treatment for 24 months.

LUNG FUNCTION AND GAS DIFFUSION STUDIES IN TREATED CASES OF PULMONARY TUBERCULOSIS

R. JAYASWAL

Sixty sputum positive cases of pulmonary tuberculosis were treated for, 3 to 9 months with short-course chemotherapy, the regimen being 2 SHRZ + 7 S₂H₂Z₂. All patients were adult males. Nearly half the patients were moderately advanced and the other half far advanced. Twenty two patients showed obstructive lung disease; 19 had restrictive disability and 8 had both restrictive and obstructive disability. Diffusion studies showed higher values in 39 patients. There was no close relationship between the age and the diffusing capacity, though the latter was more often impaired with increasing age. There was again no correlation between age and pulmonary function. An interesting observation was that many of the patients showed higher diffusion when, evaluated towards the end treatment.

PULMONARY SCINTISCANNING : VENTILATION PERFUSION (V/Q) CHANGES IN CHRONIC PULMONARY TUBERCULOSIS

M.M. SINGH. N. LAKSHMIPATI. DEEPAK TALWAR AND A. JENA

Twenty previously treated patients (5 females) of pulmonary tuberculosis with mean age of 42.4 ± 7.9 yrs. were studied by Aerosol-perfusion lung scanning. They were smear negative on three consecutive days and had moderately or far advanced disease. The Aerosol scans were performed by inhalation of Technetium (99m Tc), phytate aerosols with mass median diameter of 0.8 micron and associated S.D. of 2.0 nebulized in "Dry Aerosol Inhalation Apparatus". Perfusion scans were performed by injecting 100,000 human albumin microsphere particles labelled with 99m Tc.

Result showed the abnormality in V/Q scans to be directly proportional to the extent of the lung lesion. However, no V.Q mismatch was observed in any of the cases, indicating that the parenchymal destruction due to tuberculosis involved equally the perfusion and ventilation of the affected areas. The functional changes closely correlated with the radiological and radioisotopic assessment of the abnormalities in all the moderately and far advanced cases of pulmonary

tuberculosis. The associated COPD changes, as predicted by dynamic lung functions, underestimated the true obstructive severity of the case.

The V/Q scans in chronic pulmonary tuberculosis reflect truly the functional and physiological status of lungs, thereby correctly estimating the damage done to the pulmonary circulation and ventilation. It has a practical utility in pre-operative assessment of cases undergoing surgery.

PULMONARY HYDATID DISEASE IN SAURASHTRA

A.L. ANAND

Seventy five cases of hydatid disease were found amongst nearly 50,000 persons above the age of 15 examined by mass miniature radiography in Saurashtra. The cyst was unilateral in 72 cases; 37 of the cases were asymptomatic. Cough, haemoptysis, pain in the chest and breathlessness were common symptoms. Pneumopericyst was seen in 3 cases, lung abscess in 6 and the floating membrane in 2 cases. Treatment of choice was surgical. Except in one case where a secondary cyst appeared in the operation scar, there was no recurrence in others for a number of years after surgical removal.

PULMONARY HYDATID DISEASE

PROF. HARIHAR DAS, ET. AL.

Twenty one cases of hydatid disease were studied. Of these, 18 had a single cyst. One of the cases presented with a lung abscess Casoni's test was positive in all cases. Water lily sign was seen in one case. All the patients were treated surgically.

PULMONARY TUBERCULOSIS AS A CAUSE OF UNFOLDING OF AORTA

M. PRASAD, *et al.*

Skiagrams of 600 patients of pulmonary tuberculosis (280 males and 320 females) treated between 1970 and 1980 were reviewed for presence of unfolding of Aorta. The skiagrams of 200 healthy controls were also studied. The age range in both groups was 20-40 years. Unfolding of the Aorta was seen in 66 out of 600 patients. The rate was significantly higher than in the controls, thus confirming pulmonary tuberculosis as one of the factors associated with unfolding of Aorta. Unfolding was unrelated to the treatment and progress of the disease.

BRIEF REPORT ON THE XIVTH EASTERN REGION TUBERCULOSIS CONFERENCE

Amidst chanting of vedic hymns, Her Majesty the Queen Aishwarya Rajya Laxmi Devi Shah, President of the Social Services National Coordination Council of Nepal inaugurated the XIVth Eastern Region Tuberculosis Conference of the IUAT in Kathmandu (Nepal) on 25th November, 1985 by lighting the ceremonial lamp. The flame for lighting the lamp was presented to Her Majesty by Dr. Keith W.H. Harris, Secretary-General of the Eastern Region of the IUAT. The inaugural function was attended by about 400 delegates and a large number of distinguished guests and celebrities in the tastefully decorated Convention Hall of Hotel Everest Sheraton.

The inaugural function opened with a welcome address by the Rt. Hon'ble Mrs. Ramal Rana, President of the Nepal Anti-TB Association and the Eastern Region of the IUAT. She expressed profound gratitude to Her Majesty the Queen for her gracious presence at this function and for agreeing to inaugurate the Conference. She also thanked the distinguished guests and delegates who had responded to their invitation. Many of them had come from long distances.

Mr. D.B. Pradhan, Secretary-General of the Nepal Anti-TB Association, referred briefly to the activities of the Nepal Association which was started 32 years ago in a very modest way. It was providing X-ray and laboratory facilities to the people and also running an out-patient clinic in Kathmandu. Expansion of the activities is aimed at taking anti-TB services to the very door-steps of the persons in need. He thanked Her Majesty profoundly for the leadership and guidance which she was providing to the National Association.

Dr. Keith Harris, the Secretary-General of the Eastern Region, referred to the resolve of His Majesty's government to eradicate hunger, disease, illiteracy and poverty from the Kingdom of Nepal. It was highly gratifying that the Tuberculosis Association of Nepal under the wise leadership of Rt. Hon'ble Mrs. Kamal Rana and her associates was taking active steps to bring tuberculosis under control as quickly as possible. A large number of recognised experts from other regions were also attending this Conference in a spirit of mutual cooperation and coordination. It was hoped that the deliberations of the Conference will help not

only the host country but also other countries in the region to revamp their control programmes. He expressed sincere gratitude to the host Association for the kindness and warmth of their hospitality.

Dr. N.C Sen Gupta, President of the EUAT, conveyed to Her Majesty the gratitude of the JUAT for her gracious presence at the inaugural function and conveyed his and the JUAT's 120 members' cordial greetings to the government and Tuberculosis Association of Nepal. The most significant achievement of the Union over the year had been the ongoing efforts to mobilise funds and expertise from the developed countries for the benefit of the control programmes in the developing countries. He said that the hick of progress in some developing countries had partly been due to their failure to apply effectively the available technology, even when it was relatively simple and inexpensive. He appealed to the countries of the region to direct their attention to this pressing need establish effective and meaningful dialogue and a partnership between governmental and non-governmental organisations.

Prof G. Daddi of Itay, in his capacity as the oldest member of the IUAT present that morning, conveyed his felicitations to the Eastern Region and the host Association for hosting the Conference. He referred briefly to the fight against tuberculosis in the developing countries over the years and hoped that with international cooperation, the developing countries will also very soon be able to control tuberculosis. He thanked the host Association for inviting him to attend the Conference.

Dr. U. Ko K.o, Regional Director of the SEARO/WHO in a short message congratulated His Majesty's government and the Tuberculosis Association of Nepal for having organised this important Conference so magnificently in the beautiful valley of Kathmandu. He acknowledged the leading role played by the Eastern Region in planning strategies for tuberculosis control inspite of severe and several constraints and for supporting actively measures aimed at strengthening the various components of the control programme- The World Health Assembly had identified tuberculosis as an area of priority and suggested ways and means to develop suitable strategies for optimal achievement. The programme aimed at

stimulating governments to allocate adequate funds, to improve case-finding and treatment. BCG coverage and operational research. He was confident that in the not too distant future, tuberculosis will cease to be a major public health problem all over the world, if collaborative efforts were pursued diligently.

The Hon'ble Shri Ruddura Prasad Gin, Minister for Health, referred to the enthusiasm and selfless effort with which all social workers in Nepal were working for the well-being of the people ever since Her Majesty the Queen had graciously accepted the Chairmanship of the Social Services National Coordination Council. Control of Tuberculosis was an essential component of the primary health care programme in Nepal and was receiving top priority along with fulfilment of the basic needs of the people in respect of food, clothing, shelter, education and social security. He paid a tribute to the National Tuberculosis Association which had been supporting the National Programme by running a Tuberculosis Hospital and by organising community based projects and health education, he wished the international participants a very comfortable stay in Kathmandu and hoped that in addition to attending the Conference, they will be able to find some time to see the beautiful country as well.

Her Majesty the Queen then lighted the ceremonial lamp amidst chanting of Vedic hymns and acclamation from the audience. The function came to an end with the playing of the Nepalese National Anthem

The Organising Committee, with the assistance of Sir John Crofton of U.K. and Dr. Keith Harris, had drawn up an elaborate scientific programme extending over five days from 25th to the 29th November 1985. Sixty eight papers were to be presented but 13 authors could not attend the Conference. The main subjects that were covered were Tuberculosis Control Programme in Nepal and other countries of the Region ; epidemiology and evaluation of control programmes: problems of case-finding and case-holding: chemotherapy; health education and community involvement; bacteriology of tuberculosis: BCG vaccination and non-tuberculous respiratory diseases. There were three sessions for free communications. An important feature of the scientific programme was a special programme on health and smoking. Sir John Crofton of U.K. made a fervent plea for setting up of National Committees on Smoking in all countries of the region with a view to spearhead the anti-smoking programme. The Scientific Programme was of a very high calibre and all the sessions were well attended. The arrangements for the scientific sessions were excellent. The hosts had arranged a cultural programme on one

evening which showed the rich variety of dance and music from the various regions of the country. The programme was very enjoyable.

The Scientific Programme included a visit to the office of the Nepal Anti-TB Association on the occasion of its flag hoisting ceremony. The delegates also went round the TB Hospital in the same campus. This was followed by a visit to three health centres in the rural areas where an integrated health programme, including tuberculosis services, was being implemented. The enthusiasm and involvement of the people in implementing the programme and availing of the services was remarkable.

The Hon'ble Health Minister and the Nepal Anti-TB Association hosted dinners for the delegates and a lunch was hosted by the Kathmandu Nagar Panchayat.

The Nepal Anti-Tuberculosis Association had spared no means to make the Conference a resounding success in all respects. Arrangements for the Scientific Sessions, delegates' accommodation and transport and hospitality were excellent. The delegates were highly appreciative of the arrangements and expressed their gratitude, singly and collectively, to Rt. Hon'ble Mrs. Kamal Rana, President of the Host Association and her band of dedicated workers for all they had done.

The Conference made the following recommendations :-

- (1) Case-finding and case-holding activities must be intensified since these play an essential role in interrupting the chain of transmission of tubercle bacilli in the community.
- (2) Top priority should be given to case finding by examination of sputum. At least two sputum smears should be examined.
- (3) Health education activities should be stepped up with a view to encourage passive case-finding amongst respiratory symptomatics.
- (4) Supervisory teams should be organised at national and peripheral levels to supervise the activities of the health personnel and to provide training/re-orientation facilities.
- (5) Short-course chemotherapy has advantages over the conventional chemotherapy to the extent that it is conducive to higher completion and lower relapse rates but it

should not lead to any relaxation of case-holding efforts. Indeed, it calls for even greater efforts. It must also be remembered that short-course chemotherapy, especially if it is intermittent, may not be much cheaper since the cost of treatment is not merely the cost of drugs but also includes the cost of providing surveillance of treatment.

- (6) Only regimens of proven efficiency should be deployed for short-course chemotherapy. Regimens recommended by the Treatment Committee of the IUAT have already been published. Intermittent treatment must be administered under supervision.
- (7) The recommendations of the WHO/IUAT Expert Committee on BCG are reiterated strongly. Priority be given to coverage of infants upto one year in age.
- (8) Continuing evaluation of activities is recommended with a view to identify difficulties in the implementation of the programme and to devise solutions for the difficulties. Evaluation should be aimed mainly at determining the percentage of symptomatics amongst new patients; the percentage of symptomatics whose sputum has been examined; the percentage of sputum specimens found to be positive; the percentage of sputum positive patients starting treatment; the percentage of defaulters at various stages of treatment; the percentage of deaths in the first year, the percentage of failures of treatment (persons whose sputum remains unconverted at the end of treatment); the percentage of relapses and the percentage of false positive and false negative sputum microscopy results.
- (9) The WHO recommendations in respect of the role of voluntary organisations in supplementing the governmental efforts vis-a-vis the National Tuberculosis Programme were further endorsed.
- (10) National Associations should pay serious attention to the increasing problem of smoking and cooperate with other National Health and Consumer Associations to raise public awareness and to bring pressures on governments to implement the suggestions contained in the publications of the Smoking and Health Committees of the IUAT which will be available to member countries in March, 1986. It was also recommended that each Association should set up its own National Committee on Smoking and Health for this purpose and appoint

a 'contact person' particularly interested.

in this probe m to establish a liaison with the Central IUAT Committee on Smoking and Health.

The important decisions of the Council and the Executive Committee of the Region

- (I) It is proposed to set up a small fund to give mutual assistance for small projects being undertaken in various countries of the region and which are approved by the National Associations. The Applications for subsidy/grant for these projects will have to be routed through the National TB Associations and with the concurrence of the National governments. The subsidy will be made available from the Secretariat of the Eastern Region of the IUAT through the National Associations. Application forms will be available from the Secretariat of the Eastern Region of the IUAT.

(2) The Newsletter of the region should continue to be brought out once or twice a year. A comprehensive bulletin may be brought out once in two or three years as and when material is available. Dr. Pamra of India agreed to continue editing the Newsletter and the bulletin,

- (3) Mainland China has been officially re-admitted as a member of the IUAT.
- (4) The next Eastern Region Conference will be held in Pakistan in 1987.
- (5) The following office bearers were elected :-

President To be nominated by Pakistan

Immediate Past President

Rt. Hon (Mrs.) Kamal Rana (Nepal)

Vice-President Dr. T. Shimao (Japan)

Secretary-General Dr. Keith W.H. Harris (Australia)

Treasurer Dr. B.P. Mozoomdar (Singapore)

Representative of the Region to the IUAT Executive Committee Dr. S.P. Pamra (India)

Member

Dr. S.P. Pamra (India) Dr. Songkram Supchaioen (Thailand) Dr. J.S. Sodhy (Malaysia) Dr. Masakazu Aoki (Japan) Dr. Hong Young Pyo (South Korea) Dr. J.S. Gunardi (Indonesia)

NEWS & NOTES

ANNUAL MEETINGS OF THE T.A.I.

The 47th Annual General Meeting of the Tuberculosis Association of India was held at 11 A.M. on Friday, the 18th April, 1986 in the Conference Hall of the Association, 3, Red Cross Road, New Delhi-1. The meeting was presided over by Shri S. Ranganathan, ICS (Retd.) President of the Association and was followed by a meeting of the Central Committee of the Association.

The Conference of Secretaries of State TB Associations was held in the afternoon of 19th April, 1986. The Technical Committee of the Association on 17th April, 1986.

CHAIRMAN, TECHNICAL COMMITTEE

Dr. S.P. Gupta, Assistant Director General of Health Services (TB), Government of India, New Delhi, has been nominated as Chairman of the Standing Technical committee of the TB Association of India for 1986-87 vice Dr. D. Umapathy Rao, whose term of office expired with the 40th National Conference held in Shillong in November 1985. Dr. Gupta will also preside over the 41st National Conference on Tuberculosis and Chest Diseases to be held in Hyderabad (Andhra Pradesh) from the 25th to 28th October,

41ST NATIONAL CONFERENCE

The 41st National Conference on Tuberculosis and Chest Diseases will be held in Hyderabad (Andhra Pradesh) from 25th to 28th October, 1986 under the joint auspices of the Tuberculosis Association of India and TB Association of Andhra Pradesh. Those who wish to attend the Conference and present papers at its Scientific Sessions may kindly send two copies of the abstracts of their papers 10 days before the Secretary-General, Tuberculosis Association of India, 3, Red Cross Road New Delhi-110001, latest by the 15th June, 1986,

RANBAXY-ROBERT KOCH ORATION

The Tuberculosis Association of India has selected Dr. K. Styblo, Director of Scientific Activities of the International Union Against Tuberculosis, Paris, for this year's Ranbaxy-Robert Koch Oration which will be delivered by him at the 41st National Conference on TB

and Chest Diseases to be held at Hyderabad from 25th to 28th October, 1986.

WANDER-TAI ORATION

Dr. R. Prabhakar, Director, Tuberculosis Research Centre, Madras, has been selected for this year's Wander-TAI Oration which will be delivered by him at the 41st National Conference on TB and Chest Diseases to be held in Hyderabad from 25th to 28th October, 1986.

CHANCHAL SINGH MEMORIAE AWARD 1986

The Tuberculosis Association of India award a cash prize of Rs. 1,000/- to a medical graduate below 45 years of age and working in tuberculosis, for an original article based on the work done by the author himself, not exceeding 30 double spaced foolscap typed pages (approximately 6,000 words) excluding charts and diagrams on a subject relating to tuberculosis. Papers with more than *one* author are not eligible. Papers may be sent, in quadruplicate, to reach the Secretary-General, Tuberculosis Association of India, 3, Red Cross Road, New Delhi-110001, before the 31st of July, 1986,

ESSAY COMPETITION—1986

The Tuberculosis Association of India awards every year a cash prize of Rs. 500/- to a final year medical student in India for an original Essay on Tuberculosis, adjudged best by a Special Committee of the Association. The subject selected for the 1986 competition is 'BASIS, TECHNIQUE, INTERPRETATION AND SCOPE OF TUBERCULIN TEST'. The essay should be written in English, typed in foolscap size, double spaced and should not exceed 15 pages (approximately 3000 words excluding tables, diagrams, etc.) Four copies of the manuscript should be forwarded through the Dean or Principal of College/University to reach the Secretary-General, TB Association of India, 3, Red Cross Road, New Delhi-110001, before 31st July, 1986.

REFRESHER COURSES

Gujarat : The Gandhidham branch of the Indian Medical Association organised a refresher course on 9th February 1986 which was conducted by Dr. A.G. Patel, Chairman, Gujarat State TB Association. The course was

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attended by 33 doctors and was sponsored by M/s Themis Chemicals Ltd., Bombay.

Madhya Pradesh : The Madhya Pradesh Council, of Science and Technology, in collaboration with the District TB Association and Indian Medical Association, Jabulpur, organised a course on 9th February, 1986. Dr. S.P. Pamra, Horn. Technical Adviser, Tuberculosis Association of India, attended the course and delivered lectures on Diagnosis and Treatment of Pulmonary Tuberculosis. The course was attended by 80 doctors.

Maharashtra: The Maharashtra State Anti-tuberculosis Association, in collaboration with the Indian Medical Association, organised a course in Beed on 19th January, 1986. The course was attended by 200 doctors and was sponsored by Ms Cynamide India Limited.

Tamil Nadu: . The District Tuberculosis Association, Kamanathapuram, under the joint auspices of the TB Association of India and the Anti-TR Association of Tamil Nadu and in collaboration with the local branch of the Indian Medical Association, organised a refresher course on 2nd March, 1986. The course was sponsored by the National Academy of Medical Sciences.

XIVTH GUJARAT CONFERENCE

The XIVTH Gujarat State Tuberculosis Workers' Conference was held on 1st and 2nd March, 1986 at Surat, The Conference was inaugurated by Shri Bardolia, Mayor of Surat and the Commissioner of Surat Corporation was the Guest of Honour. Dr. P.M. Udani delivered, a Guest lecture on "Childhood TB" which was highly appreciated. About 100 doctors including District TB Officers and 500 oilier basic TB workers attended the Conference.

MADHYA PRADESH VOLUNTARY HEALTH ASSOCIATION MEETING

The 14TH Annual General Meeting of the Madhya Pradesh Voluntary Health Association was held in Bhopal on 7th and 8th February, 1986 Dr. S.P. Pamra, Hony. Technical Adviser, TB Association of India, participated in the meeting as a resource person in tuberculosis and delivered a lecture on "Management of Pulmonary Tuberculosis". The meeting was attended by about 60 delegates consisting of doctors, multipurpose health workers, health visitors, nurses, etc.

ANTI-TB WEEK

Anti- TB week was celebrated by the Ananta-

pur District TB Association from 17th to 23rd February, 1986. Shri Ashok Kumar Tigidi, Collector of Anantapur, presided over the main function which was attended by a large number of citizen of Anantapur, general medical practitioners and officers of the Medical and Health Department. The president exhorted the audience to enrol themselves as members of the Association, step up TB Seal Sale Campaign, and help in the fight against tuberculosis in general. The President also announced that facilities for indoor games for the recreation of patients will be provided at the Chest Diseases Hospital, Anantapur. A brief report on the working of the clinic was presented by the D.T.O. and clothes were distributed to 30 needy patients

Cases- finding camps were organized at five e primary health centres. viz Atmakur, Chennekoihapolli, Obuladevara Cheruvu, Mopidi and Mudigubba during the week. The newly

SYMPOSIUM

A symposium on "Recent Advances in Respiratory Diseases", was organised by the Department of Respiratory Diseases and Tuberculosis, Grant Medical College, Bombay, on 15th and 16th of March, 1986. The symposium was inaugurated by Prof. Javed Khan, Minister of State for Education, Government of Maharashtra, The symposium, was sponsored by the National Academy of Medical Sciences.

BARCLAY MEMORIAL AWARD

Dr. P.K. Sen, Emeritus Editor of the Indian Journal of Tuberculosis, has been awarded "Barclay Memorial Award" by the Asiatic Society¹ for outstanding contributions in Medical Sciences. The award was presented to him on 5th May, 1986.

OBITUARIES

Dr. M.S. Mitra of Bhopal, passed away on 19th December, 1985. Dr. Mitra was working in the Lady Linlithgow Sanatorium, Kasauli and later on served with the R.K. Mission TB Sanatorium, Ranchi and GOVT. TB Hospital, Bhopal. Just before his retirement he was the Chief Medical Officer, B.H.E.L., Bhopal. He was a sincere and devoted TB worker. The Association offers its deepest condolences to the bereaved family.

Dr. Eromus lyngdoh, Director of Health Service and Chairman, Meghalaya TB Association passed away on 11 th January, 1986. He

was a member of the Central Committee of the Tuberculosis Association of India. Dr. Lyngdoh took keen interest in developing the various activities of the Meghalaya TB Association and played a major role in successfully o

and Chest Diseases Workers held in Shillong in November last. For his outstanding contributions in the field of health, he was honoured with the award of "Padma Shri" in 1985. The Association offers its deepest condolences to the bereaved family.

POST-DOCTORAL MEDICAL RESEARCH

The National Medical Researcher Matching Programme provides opportunities in postdoctoral medical research in the United States and Canada for individuals with MD or Ph.D who are interested in conducting research in the United States or Canada. For detailed information, prospective applicants may contact: National Medical Researcher Matching Programme (Address : 1109. Main Street, Suite C Boise, Idaho 83702, USA)