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ISONIAZID IN PULMONARY TUBERCULOSIS

The announcement of the new antituberculous drug isonicotinic acid hydrazide, now known as isoniazid, was first made in the American press in February, 1952.[1] Although there was a tendency to discount journalistic enthusiasm, it was soon clear that the new drug was worth careful investigation. Great credit is due to the Medical Research Council for launching a controlled clinical trial on a wide scale by March, 1952, and to the Tuberculosis Chemotherapy Trials Committee, which has been able to complete an important preliminary report, published in our opening pages this week, six months after the start of the trial. This was achieved by the use of a system requiring continued analysis of accumulating data, and has involved an immense amount of work by those responsible for the co-ordination of the trial and the statistical analysis of the results. A tribute must also be paid to the clinicians and bacteriologists of the 39 participating hospitals in England, Scotland, and Wales, whose enthusiasm and self-discipline made the trial possible and enabled those who compiled the report to present the results so quickly.

This preliminary report, following the basic principle of earlier controlled trials by the Medical Research Council of chemotherapy in tuberculosis,[2] is a comparison of the results of treatment with isoniazid alone, in doses of 100 mg. twice a day by mouth, with those obtained by giving streptomycin, intramuscularly in doses of 1 g. daily, combined with the sodium salt of para-aminosalicylic acid (P.A.S.) in doses of 5 g. four times a day by mouth. In contrast to the previous trials, patients with pulmonary disease of a wide range of severity were included, the cases being divided into three main groups according to the acuteness of the disease. The report concerns 331 patients who have been treated for three months. Patients were allotted at random to the alternative treatment groups, 173 receiving isoniazid alone and 158 streptomycin combined with P.A.S., the range of severity in the two groups being similar. The report shows that at the end of three months' treatment the results with isoniazid are comparable to those with streptomycin combined with P.A.S. The only statistically significant difference between the two regimes was in the amount of weight gained by patients; there was significantly greater increase in those treated with isoniazid. The improvement in the general condition of the patients on isoniazid was also a little greater, perhaps owing to the absence of the nausea and anorexia often associated with P.A.S. To offset these advantages streptomycin and P.A.S. were rather more effective in reducing fever and the erythrocyte sedimentation rate, in converting the sputum from positive to negative, and in improving the radiographic appearance of the disease; but the differences are not great and are certainly not statistically significant. In patients with acute disease these differences are smaller still, or even to the advantage of isoniazid.

In the doses used, and over the period of observation, isoniazid was remarkably free from toxicity. In only one patient out of 173 was it thought necessary to stop the drug, whereas streptomycin and P.A.S. were discontinued in seven cases. A number of side-effects of isoniazid were reported, including drowsiness, exaggeration of deep reflexes, tremor of limbs, twitching of the legs, disturbances of micturition, "nervousness," constipation, transient flushing of the face, pruritus, and desquamation of the skin. This may seem a formidable list, but the effects were observed in only a small number of the patients and are such as might well be recorded in any group of patients subjected to close observation and inquiry. This view is strengthened by the variation from hospital to hospital of reports about side-effects, and by the rather different toxic reactions reported in the German[3] and Italian[4] literature.

Unfortunately isoniazid is shown to have one very grave disadvantage: drug-resistant bacilli have quickly appeared in patients being treated with it. Of those whose sputum remained positive, isoniazid-resistant tubercle bacilli were isolated from 10% after treatment for one month, from 50% after two months, and from 70% after three months. Moreover, there was less improvement in the patients from whom resistant bacilli were isolated, even allowing for the tendency for resistant organisms to emerge in the more severely ill. It seems, therefore, that isoniazid-resistance is of clinical significance. The combined use of isoniazid with streptomycin and with P.A.S.

1 See leading article in the *British Medical Journal*, 1952, **1**, 858.
2 *British Medical Journal*, 1948, **2**, 769; 1950, **2**, 1073; 1952, **1**, 1157.
3 Klee, P., *Dtsch. med. Wschr.*, 1952, **77**, 578
4 Monaldi, V., *Rif. med.*, 1952, **66**, 393.

is at present under trial, with the object of finding out if the emergence of resistant organisms can be prevented. So far isoniazid-resistant bacilli have been isolated from only two patients out of eleven treated for two months with streptomycin and isoniazid together: in both these patients the organisms were found to have been streptomycin-resistant at the start of treatment. But results in such a small number of cases can be suggestive only, and it is not yet known whether isoniazid reciprocally diminishes the emergence of streptomycin-resistant bacilli.

It is clear from this preliminary report that isoniazid is a very effective antituberculous drug, but that in view of the ready emergence of drug-resistant organisms it should in general not be given alone. Until it is determined whether either streptomycin or P.A.S., given together with isoniazid, effectively and reciprocally diminishes the incidence of resistance to both the drugs used, it will be wise not to use isoniazid even in combination except on limited indications. Gross intolerance to streptomycin or P.A.S. is one indication; though it must be remembered that most patients sensitive to either drug can be readily desensitized. Known resistance of a patient's tubercle bacilli to streptomycin or P.A.S. is a second indication, provided that chemotherapy is imperative. In such a case it is probably best to combine isoniazid with either streptomycin or P.A.S., according to which of them it is hoped the bacilli are still sensitive. Unfortunately, when streptomycin and P.A.S. have been given for long periods, tubercle bacilli found to have developed resistance to one drug will in many cases also be found to be resistant to the other. Nevertheless the combined treatment is worth trying, though at present it must be assumed that isoniazid will be clinically effective for a month or two only and must therefore be given only when chemotherapy is essential. When a patient is desperately ill and is failing to respond to streptomycin and P.A.S.—a rare occurrence in the absence of drug resistance—the administration of isoniazid in addition to the other drugs is possibly justifiable. But, for reasons which will be clear from this discussion, the use of all three drugs as a routine is undesirable: at present isoniazid is a drug to keep in reserve.

It is possible, and even probable, that this cautious view of isoniazid treatment will be modified when the results of the further trials now under way are known. Meantime those who have to treat pulmonary tuberculosis will be serving both their patients and the public by continuing to rely on the combination of streptomycin with P.A.S. for the routine chemotherapy of tuberculosis.

ELECTROENCEPHALOGRAPHY

When Professor B. H. C. Matthews succeeded his chief, Professor E. D. Adrian, O.M., in the chair of physiology in Cambridge it gave particular satisfaction to workers in the field of electroencephalography, with which these two names will always be linked. Their past collaboration has produced work of great scientific excellence, but none with such far-reaching results as their confirmation of the work of Hans Berger—the observation that the electrical activity of the human brain could be recorded from the intact scalp. The recent award of a knighthood to Professor Matthews, though for work of another kind, is a not inappropriate occasion to consider the history of electroencephalography in this country and its present position here.

Soon after publication of Adrian and Matthews's work reports began to appear on the possible clinical uses of E.E.G., and by the beginning of the second world war the fundamental human norms were well established, and various changes associated with epilepsy and with structural cerebral damage were recognized. Laboratories in America and many European countries were actively concerned in this pioneer observational work. Its growth was brought to an abrupt halt by the war everywhere except in the U.S.A., where commercially made apparatus of good quality continued to be available and the demands on the research workers were, for a while at least, less pressing. In this country the requirements of radar and radio communication made it impossible to obtain new apparatus, so that during the war years and for some time afterwards very few new centres were set up and few new workers entered the field. Nevertheless there were enough to form a discussion group, which in 1945 became the E.E.G. Society, the first of its kind. This example was followed shortly in the U.S.A., which has both a national and regional societies, and by half a dozen other countries. Thanks to the energy of Dr. Grey Walter, who had been largely responsible for forming the Society, the first international congress was held in London in 1947, followed by the second in Paris in 1949. As a result of these congresses the subject now has an International Federation, which is affiliated with Unesco, and owns the very flourishing *Electroencephalography and Clinical Neurophysiology*. The third international congress is due to take place next summer in Boston.

Great Britain has thus played an active part in the development of clinical electroencephalography and has made technical and clinical contributions of the first importance, but there is no cause for com-