Although it would appear that in the U.S.A. many tracheotomized patients have learned G.P.B., we have not so far succeeded with two patients now on intermittent positive pressure breathing. There are difficulties in preventing leaks from the tracheostome which could be minimized by using suitable plugs as recently developed in the U.S.A. (Dail, personal communication, 1957). These patients, we think, are psychologically ill-adapted also, particularly where they have been for a long time "addicted" to intermittent positive pressure breathing.

A patient cannot eat during frog-breathing. However, one of our patients (Case 1) uses her accessory muscles of respiration while masticating and returns to frog-breathing after she has swallowed. With this combination she can consume an average meal in less than half an hour.

If illness develops, the energy required to perform G.P.B. may be lacking and the patient will require assistance by artificial respiration.

The presence of an irritant—for example, food particles or mucus near the glottis—may cause guarding and temporarily diminished ability for efficient G.P.B. An assistant may be required to help by chest squeezing during expiration to facilitate its dislodgment.

Glossopharyngeal breathing may be regarded as a form of intermittent positive pressure respiration. If the inspiratory phase is prolonged the venous return to the heart is progressively reduced as the intrathoracic pressure rises; thus the cardiac output progressively diminishes, and it has been observed to coincide with a reduction in blood pressure. Most patients complain of lightheadedness for a few seconds after maximal G.P.B., presumably due to transient cerebral anaemia. However, when G.P.B. is carried out to provide maintenance tidal exchange there appears to be no lessening in cardiac output. Dail and his co-workers (Collier *et al.*, 1956) maintain that if the tidal exchange is kept below one litre, provided also that the inspiratory phase is not very prolonged, there is no significant change in cardiac output.

Summary

The usefulness of glossopharyngeal breathing (G.P.B.) in chronic poliomyelitis patients with respiratory paralysis is described. Case reports of six patients from this hospital who have learned the technique are presented and the value of G.P.B. is analysed in each case.

The basic advantage of G.P.B. is the enhanced ability of the patient to increase his vital capacity, which makes him less dependent on respirators and increases his power to cough and stretch his chest. The social and psychological advantages of this type of breathing are stressed.

It can be concluded, without reserve, that G.P.B. is of great value to seriously handicapped patients and that more use of this technique should be made in all centres where post-acute and chronic poliomyelitis patients are cared for.

We wish to record our thanks to the staff and patients of the poliomyelitis unit for their help and co-operation in this study. Our thanks are also due to Mr. E. J. Tunnicliff, of Electronic and X-ray Applications Ltd., London, for loan of the Monaghan spirometer with which many of the measurements were made.

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PSYCHOSIS DUE TO ISONIAZID

BY

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During the five years in which isoniazid has been in general use in the treatment of tuberculosis, the only toxic manifestations frequently reported have been those involving the central nervous system. A few cases of encephalitis have occurred (Biehl and Nimitz, 1954; Mitchell, 1955) which may or may not have been due to the drug, but peripheral neuropathy and psychosis are both well-recognized side-effects which have not infrequently been encountered. Most attention has so far been focused on neuropathy, although it is usually only seen in those patients receiving dosage much larger than normal. Apart from cases with paraesthesia only, peripheral neuropathy must be exceedingly rare when isoniazid is given in conventional dosage (2–5 mg./kg.). On the other hand, where psychosis has been reported the relation to dosage is less obvious. In the M.R.C. (1952) trial, in which 173 cases received 200 mg. of isoniazid daily, there were no reports of peripheral neuritis, but four cases developed nervous symptoms, in one of which these were persistent and severe enough to warrant stopping the drug and withdrawing the case from the trial. The purpose of this paper is to record five cases developing a psychosis whilst receiving isoniazid in dosage well within the normally accepted range.

Summary of Cases

Case No.	Duration of Isoniazid Before Onset	Dosage of Isoniazid (mg./kg.)	Possible Predisposing Factors	Predominant Mental Symptoms	Treatment	Duration of Psychosis After Isoniazid Withdrawn
1	34 weeks	3·8	Oxytetracycline. P.A.S. intolerance	Hysteria	Nil	6 weeks
2	3–4 ,,	4·5	P.A.S. intolerance	Mania	I.M. vit. B complex; good response	8 months
3	7–8 ,,	2·6	Nil	Anxiety with paranoid symptoms	Nil	3–4 ,,
4	1 week	2·9	,,	Schizoid reaction	I.M. nicotinic acid; partial response. I.M. vit. B complex	5 weeks
5	6–8 weeks	3·2	Chronic alcoholism. Oxytetracycline. Chlortetracycline	Depression	I.M. nicotinamide; good response	1 week

Case 1

A scaffolder aged 53 was admitted to the ward in July, 1954, with a cavity in the right upper lobe and a positive sputum. He had a long history of basal bronchiectasis with a recent acute episode treated with oxytetracycline. His general condition was, however, good and he was not appreciably toxic. He was given a 60-g. course of daily streptomycin with P.A.S. followed by isoniazid, 200 mg. daily (3.8 g./kg.) with P.A.S. After three months the P.A.S. was replaced by streptomycin owing to some mild gastric upset, but progress was otherwise satisfactory and he was co-operating well. In mid-January he complained of

transient paralysis down the right side and a sensation of butterflies in the stomach. No neurological signs could be elicited, except that reflexes were all very brisk. Thereafter he showed increasing mental change, becoming resentful and argumentative. Hysteria was diagnosed and he was sedated with phenobarbitone. A month later the "paralysis" recurred. The only change in the C.N.S. was that ankle clonus was now present. His mental state had not improved. He remained in a state of tension, constantly complaining about trivialities, and was difficult to manage in the ward.

All chemotherapy was then stopped and over the following six weeks his mental outlook slowly returned to normal. During this period of mental upheaval his cavity had closed and no further chemotherapy was given. He was eventually transferred to a rehabilitation settlement, where he has done well.

Case 2

An aircraft fitter aged 39 developed infiltration in the left upper zone in December, 1954. Sputum was positive for acid-fast bacilli. On admission to the ward his condition was good, he was not toxic, and he appeared normal mentally. From January 3 to March 22, 1955, he received a course of twice-weekly streptomycin with P.A.S. Owing to mild gastro-intestinal disturbances the chemotherapy was then changed to streptomycin, 1 g. three times weekly, and isoniazid, 300 mg. (4.5 mg./kg.) daily. Over the next 10 weeks he became increasingly talkative, until it was quite impossible to nurse him in the general ward and he had to be moved to a side-ward. He was euphoric and had grandiose ideas of his own capabilities and resources. Chemotherapy was stopped on May 26; on June 6, before psychiatric aid was forthcoming, he discharged himself from hospital.

Two weeks later he attended the Chest Clinic and was still talkative, euphoric, and somewhat facetious, though there was also some insight into past events. In spite of his zest for conversation, his expression was noticeably clumsy. There had been continuous and satisfactory regression of his tuberculosis. In another month there was some mental improvement, though he was still talkative and excitable. In August a course of streptomycin and P.A.S. was begun and he remained in bed at home.

In January, 1956, his wife complained about his behaviour. From a quiet disposition prior to his stay in hospital his personality had completely changed and he had taken to asserting himself in demonstrative and sensational ways. On interview he seemed rational, but obviously was still tense and loquacious. It was then decided to try the effect of intramuscular "parentrovite,"* a vitamin B concentrate, and 5 ml. was given twice weekly for three weeks. Within one week there was noticeable improvement, and within two months he was back to his normal quiet and relaxed temperament. Subsequently long courses of streptomycin and P.A.S., and isoniazid and P.A.S., were given, but no relapse was provoked.

Case 3

A tool-grinder aged 37 was admitted to hospital in May, 1955, in a toxic condition with a cavitated lesion in the right upper lobe and strongly positive sputum. After six weeks of streptomycin, 1 g. twice weekly, isoniazid, 200 mg. daily (2.6 g./kg), and P.A.S., 15 g. daily, his temperature became normal. There had been no sign of mental instability. Chemotherapy was then changed to streptomycin, 1 g. daily, with isoniazid, 200 mg. daily. A few days later he complained that the other patients were whispering about his chest condition and that he feared that they would smother him with a pillow. He took his own discharge from hospital shortly afterwards. Chemotherapy (streptomycin 1 g. four times weekly with isoniazid 200 mg. daily) was restarted at home on June 29, three days after his self-discharge. On July 5 he attended the Chest Clinic in a highly nervous state, although he himself claimed to be back to normal, and he displayed considerable insight into his previous aberrations.

When seen again a month later he had obviously relapsed into an acute anxiety state. He appeared apprehensive and fidgety and said he had completely lost confidence in himself. There was, however, no recurrence of paranoid delusions. Isoniazid was stopped immediately and replaced by P.A.S., 20 g. daily. In a month he was much improved, and within four months was back to his normal self. Subsequently he received several long courses of streptomycin and P.A.S. (but not isoniazid), was readmitted to hospital, and had a two-stage thoracoplasty without any recurrence of anxiety symptoms.

Case 4

A draughtsman aged 17 was admitted to hospital on October 3, 1955, with a cavity at the right apex which had failed to respond to a three-months course of streptomycin and P.A.S. at home. He had a low-grade temperature, his general condition was good, and mentally he appeared to be a normal and intelligent youth. Streptomycin, 1 g. four times weekly, and P.A.S., 15 g. daily, was continued and he was postured for the apical cavity. On November 15 P.A.S. was replaced by isoniazid, 200 mg. daily (2.9 g./kg.). About a week after the course started an acute confusional state developed. Anxiety was the predominant mood, but he also had complex delusions, including the conviction that he was changing sex. Insight into his condition was only partial. Neurological examination was negative, apart from a generalized increase of tendon reflexes. The C.S.F. showed a slight increase of protein (65 mg.) with slight excess of globulin.

A psychiatrist to whom the patient was known personally considered that his condition was compatible with a toxic psychosis due to drugs. Isoniazid was discontinued soon after the onset of the mental change and from November 25 nicotinamide, 100 mg. three times a day, was given for seven days. Prompt improvement in his mental state occurred, although his behaviour remained a little childish and emotionally overcharged. Towards the end of December delusions recurred, though of a milder character. The C.S.F. was unchanged and there were no fresh neurological signs. Parentrovite, 2 ml. intramuscularly on alternate days, was given over a period of four weeks, and within a week his mental state was completely normal. Chemotherapy (streptomycin and P.A.S.) was restarted in January, 1956, and in spite of repeated courses, which included isoniazid at a later date, and in spite of the ordeal of a major surgical operation (lobectomy) there has been no further mental relapse.

Case 5

A professional man aged 52 had had extensive cavitated disease since 1948 and was an alcoholic. He was nevertheless a good chronic case and was able to carry out his professional duties. The only previous chemotherapy was a three-months course of streptomycin and isoniazid in 1953. He was admitted to a general hospital in August, 1955, with collapse/consolidation of the right lung following fracture of ribs by a fall. There was a partial response to courses of penicillin, oxytetracycline, and chlortetracycline (the latter two antibiotics causing some diarrhoea), but it then became obvious that there was also an exacerbation of the tuberculous disease. Streptomycin, 1 g. daily, and isoniazid, 200 mg. daily (3.2 g./kg.), were started on September 10, but, owing to streptomycin resistance, viomycin, 4 g. weekly, and P.A.S., 15 g. daily, replaced streptomycin on October 6. Isoniazid was continued in spite of partial resistance to the drug.

Over the next four weeks the patient developed increasing mental lethargy and depression, although there was coincident improvement in his temperature and chest *x*-ray picture. He seemed incapable of helping himself and had to be

*Parentrovite: aneurine 250 mg., nicotinamide 160 mg., riboflavine 50 mg., pyridoxine 50 mg., calcium pantothenate 5 mg., ascorbic acid 500 mg.

fed at every meal. His reaction time was excessively slow and he was grossly disorientated in time. Examination of the C.N.S. was normal except that the reflexes were on the brisk side. Without stopping his drugs intramuscular nicotinamide, 100 mg. daily for seven days and 50 mg. daily for seven days, was started on November 24. The improvement was dramatic and almost immediate, the depression and lethargy disappearing within a week. On discharge three weeks later he was mentally alert and cheerful. A further course of isoniazid was given at a later date without untoward effect, the patient receiving simultaneous vitamin B complex supplement to the diet.

Discussion

The mental changes shown in these cases are all compatible with a toxic psychosis, the precise form of the disorder being dependent on the previous constitutional make-up and personality of the patient. Although direct evidence implicating isoniazid is perhaps not overwhelming in every case, by inference it is strong because of the absence of any previous mental breakdown and because of the similarity to other reported cases.

Deprivation of vitamin B is the generally accepted mechanism involved in both peripheral neuropathy and psychosis due to isoniazid. Biehl and Vilter (1954), investigating peripheral neuritis occurring after high isoniazid dosage, were impressed by the similarity of the picture to that produced by the pyridoxine antagonist desoxypyridoxine. Moreover, they found that neuropathy did not develop if pyridoxine, 50 mg. daily, was given with the isoniazid. Instead of the theory previously put forward of competitive blocking of pyridoxine by the similar isoniazid molecule, they considered that isoniazid interacted with vitamin B_6 in the tissues to form a pyridoxal isoniazid complex which they found excreted in the urine in large quantities. This was confirmed by Williams and Abdulian (1956), and these authors and Vilter (1955) have drawn attention to the increased excretion of xanthurenic acid in the urine which occurs with pyridoxine deficiency and consequent failure of the enzyme system responsible for tryptophan breakdown, in which pyridoxine plays a part. Vilter claims to have demonstrated this more clearly by giving a 10-g. loading dose of tryptophan and finding a gross excess of xanthurenic acid excretion in such cases.

Other clinical evidence in favour of a simple pyridoxine deficiency is less certain. One of the two cases of peripheral neuropathy described by Jones and Jones (1953) responded to nicotinamide alone, and two of eight cases in alcoholics taking isoniazid reported by Oestreicher *et al.* (1954) failed to improve with pyridoxine. Wood (1955) reported five cases of psychosis and 13 cases of pellagra amongst Bantu, presumably all in poor nutritional state, receiving isoniazid dosage varying from 8 to 12 mg./kg. Three of the psychotics recovered completely with nicotinic acid alone. Three of the pellagra cases also recovered with nicotinic acid alone, but in others improvement was only partial until other B complex vitamins were given. McConnell and Cheetham's (1952) case of pellagra and psychosis occurring in a patient with tuberculous peritonitis in relapse and Zabad's (1953) case of psychosis both responded dramatically to parenteral nicotinic acid. In the series described in this paper Case 5 responded satisfactorily to nicotinamide, Case 4 responded partially to nicotinamide but only completely after vitamin B complex had been given, whilst Case 2 was given vitamin B complex throughout. It is therefore unlikely that isoniazid toxicity can be attributed to one single member of the vitamin B complex, though there is ample confirmation that thiamine plays no part (Jones and Jones, 1953 ; Wood, 1955).

These problems are perhaps rather academic, and a matter of more practical importance is the question why only certain patients appear to develop C.N.S. toxicity. Biehl and Vilter (1954) give the incidence of peripheral neuropathy as 2–3% amongst those receiving normal dosage (2–3 mg./kg.), a figure which from personal experience appears to be much too high. It may be worth noting, however, that increase of tendon reflexes occurs in a high proportion of patients receiving isoniazid. It occurred in 13% of M.R.C. (1952) cases, and this may well have been an underestimate. It was a striking finding in at least two of this series and has been noted by many others (Hunter, 1952 ; Katz *et al.*, 1954 ; Wood, 1955). Its significance is doubtful, but it has been recorded as an early sign in nicotinic acid deficiency (Brain, 1947), and it is possible that a subclinical deficiency state exists in many more persons than show overt toxic signs.

Dosage, although not a factor in this series—none of the patients having received more than 4.5 mg./kg.—seems undoubtedly of much importance in the published cases of peripheral neuritis. Biehl and Vilter (1954) give an incidence of 40% in patients receiving 20 mg./kg. Wood's cases of psychosis received 7–12 mg./kg. On the whole, the dose relationship appears to be less significant in psychosis than in peripheral neuritis, but it is doubtful if this alone points to any fundamental difference in the mechanism of the two conditions.

Obviously, if vitamin B deficiency is responsible for the toxicity, anything reducing the intake of this vitamin will predispose to a reaction. Malnutrition from various causes, such as extensive tuberculous disease, poverty, and alcoholism, has featured in cases in the literature. In Case 5 in this series the patient was a definite chronic alcoholic, and in Case 1 alcoholism may also have been a factor. With modern chemotherapy, bowel upsets often occur, and P.A.S., for instance, causes diarrhoea, which may be tolerated for long periods by patients and which is bound to upset absorption of essential food factors. Both Cases 1 and 2 had difficulty taking P.A.S. The tetracyclines are known to interfere with the normal bacterial flora of the intestine, and, as intestinal bacteria may be responsible for supplying some of the body's nicotinic acid and pyridoxine, courses of these antibiotics may predispose to isoniazid toxicity. Cases 1 and 5 both received oxytetracycline prior to taking isoniazid. This leaves Cases 3 and 4, in which there was apparently no reason to expect any interference with vitamin absorption ; and probably in all the cases, except Case 5, other unknown factors must have been operating.

It is premature to advise giving vitamin B supplements to all patients receiving isoniazid, at any rate in those taking conventional doses, but nervous reactions are probably more common than is realized, and if suspected should be treated promptly. It is particularly important to consider an isoniazid reaction in any patient showing an unexpected and peculiar mental change, especially where there is no past history of mental instability. Perhaps it may also account for some of the reported increase of self-discharges from sanatoria—and two of the present series came to notice for just this reason. Treatment should be given with vitamin B complex, including nicotinamide, pyridoxine, and pantothenate. The dosage should be massive, and, in view of a possible impairment of absorption from the alimentary tract, should be given parenterally. Fortunately, it seems that, once the patient has been saturated with vitamin B complex, further courses of isoniazid can be given with impunity. This was seen in Cases 2, 4, and 5 in this series, and was also observed by Wood (1955) in most of his cases of psychosis and pellagra. No doubt it would be advisable to continue with supplements of vitamin B in the diet.

Summary

Five cases of psychosis are described in patients receiving isoniazid in the usual dosage range of 2–5 mg. per kg. Three of the cases responded completely to vitamin B complex. The role of this substance in the production of the nervous side-effects of isoniazid is discussed.

I should like to thank Dr. J. T. Nicol Roe and the staffs of the Uxbridge Chest Clinic and Mount Pleasant Hospital, Southall, for assistance in preparing this paper. I am also

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TREATMENT OF OPHTHALMIC ZOSTER WITH PREDNISONE

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Herpes zoster affecting the first division of the trigeminal nerve is a severe and painful condition, particularly in elderly patients. In many cases it is complicated by ophthalmic lesions and is often followed by intense neuralgia. There is usually considerable oedema of the face in the early stages, and some of the pain occurring before, during, and after the eruption may be peripheral in origin. It is possible that the cellular reaction to the zoster virus both intraneurally and extraneurally accounts for some of the pain, and, if so, any successful control of this reaction would be useful.

Suppression of cellular reaction by corticosteroid drugs is seen to best advantage in the allergic hypersensitivity states, but it is also known that these drugs can inhibit primary tissue responses to infection, and it was therefore thought justifiable to try their effect on ophthalmic zoster. To avoid sodium and water retention due to treatment, prednisone rather than cortisone was used.

Material and Method of Treatment

Fifteen consecutive cases of herpes ophthalmicus were treated during 1956, eight of them in the Ashford Hospital, Middlesex, and seven in their homes. Details of the treatment are as follows:

Systemic.—(1) Prednisone, 10 mg. six-hourly by mouth for four days, followed by 10 mg. eight-hourly for the next three days. The dose is then reduced by 5 mg. each day until it is discontinued on the fifteenth day. (2) Tetracycline, 250 mg. six-hourly by mouth for seven days. (3) Vitamin-B complex ("becosym"), two tablets three times a day for seven days.

Local.—(1) To the rash, oxytetracycline cream 1% daily. (2) To the eye: atropine 1%, sulphacetamide 30%, hydrocortisone 1%, applied as drops six-hourly for the first week and then according to the condition of the eye.

Results

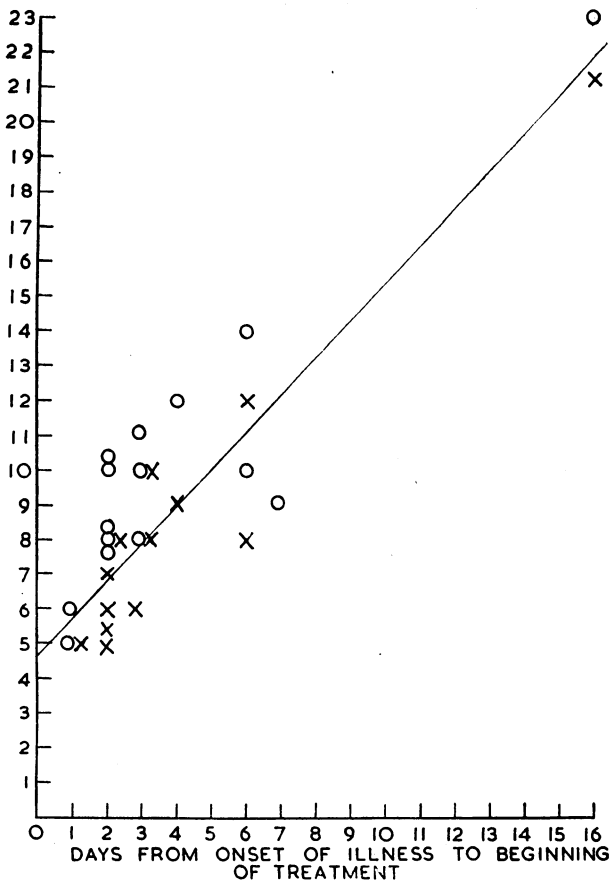
The results of treatment in these patients, although the follow-up times were short and varied from 18 to 6 months, were sufficiently satisfactory to consider that the natural history of ophthalmic zoster had been altered for the better. A previous group of 44 cases of zoster, including by chance exactly 15 cases of ophthalmic zoster, had been reported by one of us (Barham Carter, 1951), and this group was thought to be similar enough to act as a reasonable control series.

TABLE I.—*Comparison of Control and Treated Groups*

	No. of Patients	M.	F.	Average Age	Average Age of Rash on Admission
Control group, 1951 ..	15	8	7	64 years	4·3 days
Treated group, 1956 ..	15	7	8	66 ,,	4 ,,

Table I compares the two groups regarding age, sex, and duration of illness before admission to hospital. Both groups were nursed in the same wards of the same hospital under the care of the same physicians. The criteria chosen for comparison were: time of subsidence of oedema; time taken for drying of rash; appearance of fresh lesions; degree of scarring; percentage of ophthalmic complications; and severity and duration of pain, including occurrence of post-herpetic neuralgia. Tables II and III show in detail the results and progress of the two groups.

Subsidence of Oedema.—In the control series the periorbital oedema lasted from 8 to 17 days, and in the prednisone series its duration depended entirely on when treatment was begun. In Cases 5 and 13 treatment was started on the second day of the pain and within 24 hours of the rash, and no oedema appeared at all, and in Case 6 prednisone was started on the third day of the rash and the oedema lasted only for five days. In contrast one patient was admitted on the 16th day of her illness and her oedema



Scatter diagram showing relationship between improvement of rash and time of treatment. O=First day of dry rash (15 patients). X=First day free of oedema (13 patients, as Nos. 2 and 5 had no oedema).