persisted, accompanied by abundant sweating and a disagreeable odour. The special odour struck the patient and his attendants. These pale and limp patients showed inconspicuous trembling of the extremities: they complained of disorders of visual accommodation and especially of being unable to read.

The Severe Cases

For many of these patients the illness went no further than that: after suffering from insomnia for several days, the ability to sleep again was the sign of their recovery. For the others, remission of digestive disorders was only a 48-hours lull before the appearance of more characteristic signs. Even about six days afterwards, in some of the patients, more severe disorders appeared, and the vasomotor phenomena became worse. Formication, with pallor and cold in the extremities, recalled Raynaud's syndrome. Hands and feet were equally attacked; painful paraesthesias and cramps of the calves followed, aggravated by the weight of the sheets. Some of the patients had severe fainting attacks with imperceptible pulse, low and feeble arterial tension, and a feeling of anguish which often went spontaneously. Between these crises we noticed in some cases hypertensive attacks (190/100 mm. Hg); they seemed to be generalized vasomotor crises.

Neurological examination was poor but showed most often the following signs: intentional tremor was nearly always found; it was sometimes accompanied by fibrillary twitching, and there was a suggestion of myoclonus. In several unusual cases there seemed to be a cerebellar syndrome. Romberg's sign was never seen. The reflexes were slightly exaggerated, especially the patellar. In six cases we noticed a transient Babinski reflex. There was no paralysis. The mydriasis disappeared, but accommodation remained difficult.

Logorrhoea, psychomotor agitation, and absolute insomnia always presaged the appearance of mental disorders. Towards evening visual hallucinations appeared, recalling those of alcoholism. The particular themes were visions of animals and of flames. All these visions were fleeting and variable. In many of the patients they were followed by dreamy delirium. The delirium seemed to be systematized, with animal hallucinations and self-accusation, and it was sometimes mystical or macabre. In some cases terrifying visions were followed by fugues, and two patients even threw themselves out of windows. The delirium was of a confusional kind which could be interrupted for some moments by strong stimulation. Every attempt at restraint increased the agitation. In severe cases muscular spasms appeared, recalling those of tetanus, but seeming to be less sustained and less painful. During this stage, sweating was abundant, and the temperature somewhat raised. The duration of these periods of delirium was very varied. They lasted several hours in some patients, in others they still persist. As the illness developed, certain visceral signs were noted: albuminuria, sometimes with haematuria. On the other hand, the blood urea often rose to 60–120 mg. per 100 ml.

Fatal Cases

Such were the signs observed in general. Many of the patients did not show the signs and symptoms in their entirety. Most of the cases were limited to digestive disorders, insomnia, and slight disturbance of the

autonomic nervous system. About 25 cases were of the severe delirious form. We observed four fatal cases—three men and one woman. Three of these people were old and in bad health. The woman had hyperthyroidism. One of the men was only 25 years old and had been in good health previously. They died in muscular spasm and in a state of cardiovascular collapse. The blood urea was raised to 150 mg. per 100 ml. The woman showed at her death a moist gangrene of the toes.

The disorders developed more quickly in children, but also left them more quickly. In two cases we observed epileptiform convulsions, controlled by barbiturates.

An interesting feature of some cases was that the delirium was the first serious sign to be noted; it then appeared very late—between 10 to 12 days after the first onset of poisoning. It is difficult to know just how many people presented with only slight disorders—disturbances of digestion and sleep—but it was about 150. A pregnant woman was seen with frank haemorrhages, and several women menstruated prematurely.

Now that we have gathered the documents together, 15 days after the poison was taken, it is still too soon to give a definite balance sheet. Nevertheless, we can foresee the complete disappearance of the vascular disorders, but we cannot say what the effect will be on the minds of some of the patients, in particular on the minds of alcoholics who fell victims to the poison.

Medical Memoranda

Deafness from Dihydrostreptomycin

In the *American Review of Tuberculosis* of January, 1951, there appears a note on an article about "Lange Kuren" by J. E. Minkenhof (*Ned. Tijdschr. Geneesk.*, 1950, **94**, 2129). In this note it is stated that dihydrostreptomycin is more toxic than streptomycin; at the same dosages it was found that in adults, but not in children, dihydrostreptomycin caused partial to total deafness in a very high percentage of patients. The statement warrants widespread publicity; for, to say the least of it, it is most distressing to save a child from tuberculous meningitis only to render him or her totally deaf, especially if this can be avoided.

Material

In August, 1949, a 25-bed unit was established in this hospital for the treatment of tuberculous meningitis and military tuberculosis. Thirty cases of the former have been treated and four cases of the latter. Intensive antibiotic therapy has been used in all cases. For an adult with meningitis the course of treatment was: First course, 2 g. daily in two doses by intramuscular injection for four months, and 100 consecutive intrathecal injections of 50 mg. daily. A rest period was then given which varied from 14 to 28 days, depending on the rapidity of response to the first course. The second course consisted of 2 g. daily in two doses by intramuscular injection for three months, and 50 intrathecal injections of 50 mg. at two-day intervals. Appropriate reductions in dosage were made according to age and not

to individual body weight, a standard reduction being made for each age group. This was done to facilitate the work of the ward staff by reducing the number of variations of dosage to the smallest possible.

For an adult with miliary disease without meningitis a four-months intramuscular course of 2 g. streptomycin daily was given. This was followed by a rest period of one month and a second course of intramuscular streptomycin for one month. P.A.S. was usually given throughout the stay in hospital.

In July, 1950, dihydrostreptomycin replaced streptomycin in the hospital.

Analysis of the 34 Cases Treated

		Death	Recovery
Tuberculous meningitis	Treated with streptomycin	3	14
	Treated with dihydrostreptomycin	5	8
Miliary tuberculosis	Treated with streptomycin	—	3
	Treated with dihydrostreptomycin	—	1

All the recovered cases treated with streptomycin have now been discharged, except two who are still in hospital simply because home conditions are unsuitable. All these cases have been carefully followed up to the present and every patient can hear a forced whisper at 12 feet without any difficulty. It may be stated that the services of an otologist have not been available, and a scientific assessment of hearing acuity has therefore not been possible.

Cases of Deafness

Of the cases treated with dihydrostreptomycin, there have been four in whom marked impairment of hearing has occurred either during treatment or soon after the completion of treatment.

Case 1.—A girl aged 17. She responded to treatment slowly, and a positive culture of tubercle bacilli was obtained four months after the beginning of treatment. At about the fifth month of treatment she became totally deaf within 14 days. No evidence of other cranial nerve involvement of any kind has ever been obtained. She now appears well, though she continues on treatment. She remains totally deaf.

Case 2.—A girl aged 6 years. She made an uninterrupted recovery from her meningitis without incident. During the second month of her second course of treatment with dihydrostreptomycin she became totally deaf within four days.

Case 3.—A girl aged 8 years. She made an uninterrupted recovery without incident and was first noted to be partially deaf one month after discharge from hospital at her re-examination.

Case 4.—A boy aged 8 years. He also made an uninterrupted recovery, but was first noted to be partially deaf at re-examination one month after discharge from hospital.

Comment

The degree of deafness in all four cases is now gross. It is a nerve deafness. The loss of hearing in the first two cases was extremely rapid. In the second two cases it seems likely that it has been extremely slow. We now feel that the impairment of hearing probably began during treatment, but that the degree of impairment remained so slight that it was not detected by our crude tests until one month after discharge. This suggests that, once the auditory nerve has been damaged by the

drug, progressive impairment of hearing may occur after all dihydrostreptomycin therapy has ceased.

Case 1 did not respond satisfactorily to treatment, and it was at first felt that her deafness might be attributable to the meningeal process. However, the response to treatment in the other three cases was highly satisfactory. In none of these four cases has there ever been any evidence of paresis of other cranial nerves.

Case 3 has recently been seen by an otologist, who states that a gross degree of nerve deafness is present, but that this could result from the meningeal process. However, it is striking that among 14 recovered cases treated with streptomycin there has been no case of deafness of any degree. Also, in three of the cases in which deafness has occurred after treatment with dihydrostreptomycin the impairment of hearing has appeared late in the course of treatment or after treatment was completed, and it seems unlikely that the meningeal process can therefore be blamed. Only one case of miliary tuberculosis has been treated with dihydrostreptomycin, and without evidence of impairment of hearing.

The evidence therefore strongly suggests that the deafness has been caused directly by the dihydrostreptomycin. There appear to be no grounds for continuing to treat cases of tuberculous meningitis with dihydrostreptomycin rather than streptomycin.

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Case of Coma Associated with Ketonuria in a Young Adult

The following case seems to be unusual enough to merit recording.

Case Report

A male student, aged 22, at a teachers' training college was admitted to hospital on January 16, 1951, as an emergency in a state of semi-coma. Thirty-six hours previously he had been taken ill, with colicky abdominal pains, had vomited twice, and subsequently had felt better. He slept well that night. Next morning he became stuporous and was difficult to rouse. The colicky abdominal pains returned. He had had no bowel action for two days.

When seen after admission he was lying in a comatose condition on his side with his knees drawn up. There was marked air hunger, and his breath smelt strongly of acetone bodies. His temperature was 98.4° F. (36.9° C.), pulse 70, and respirations 22. He could be roused, but his cerebration was slow, and he answered only in monosyllables and at once relapsed into coma. His tongue was coated and dry; his colon was loaded. His urine gave strongly positive reactions to the ferric-chloride and Rothera tests, but no albumin or sugar was present. His other systems revealed no abnormality. His appearance was that of a diabetic coma, but his blood sugar was 90 mg. per 100 ml.

With general treatment he fully recovered in 48 hours and was then able to give a proper history. Three days before admission there had been a very fatty joint of beef for lunch: most of his friends had left the fat on their plates, and he had collected and eaten it all, as "he did not like waste."

It is to be presumed that this large amount of fat, to which he was unaccustomed, produced the ketosis. He stated that he was said to have suffered from acidosis as a small boy.

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