Commentary

I do not think that the intravenous glucose is the factor concerned, as in several cases where the patient received only natural diphtheria antitoxin without glucose (not included in this series) no reaction occurred. It would therefore appear either that streptococcal antitoxin is more toxic than diphtheria antitoxin on intravenous injection or that the sensitivity of patients to foreign protein differs in the two diseases. The time taken for the membrane to separate and the duration of the albuminuria—which latter is an index of persisting toxaemia—were also tabulated, but they showed no significant difference with the two types of sera.

As a result of this investigation we have decided in future to use natural diphtheria antitoxin for intravenous injection. The smaller bulk of the concentrated serum is still to be preferred for intramuscular injection in the milder cases.

Conclusions

When given intravenously with 20 per cent. glucose, (1) the therapeutic effects of natural and concentrated diphtheria antitoxin on the death rate and paralytic complications are equal; (2) concentrated antitoxin is twenty times as likely to give severe immediate reactions and one and a half times as likely to give late serum rashes as whole natural antitoxin. (3) On this account natural diphtheria antitoxin is to be preferred for intravenous injection. (4) These findings are not applicable to streptococcal antitoxin.

TREATMENT OF PELLAGRA WITH NICOTINIC ACID

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The work of Elvehjem and his associates (1937) on the treatment of canine black-tongue with nicotinic acid, and the resultant cures, have stimulated clinicians to use this substance in the treatment of human pellagra. Fouts and his co-workers (1937) reported four cases treated with nicotinic acid. These patients, after having been placed on a control diet poor in the pellagra-preventing factor, were observed for three days. During this time their condition remained stationary or became worse. Treatment was then begun with nicotinic acid in doses varying from 0.5 gramme to 1 gramme daily. Within forty-eight hours after the initiation of the treatment all the patients showed distinct improvement in their general condition and the stomatitis was completely healed. In two patients suffering from diarrhoea normal stools were obtained on the third and the fifth day respectively. The dermatitis disappeared within six to twenty-five days. All the patients noticed warmth and tingling of the skin ten minutes after ingestion of the nicotinic acid.

Almost simultaneously, Spies, Cooper, and Blankenhorn (1938) reported eleven cases of pellagra placed on basic control diets poor in the pellagra-preventive factor. The most striking effects were observed on the glossitis and stomatitis, which usually disappeared forty-eight hours after the beginning of treatment. The pellagrous glossitis, stomatitis, ptyalism, urethritis, and proctitis did not reappear while the patients received nicotinic acid. In one case the glossitis and stomatitis, which had disappeared with the use of nicotinic acid, recurred when it was discontinued. Mild cases of dermatitis in which the epithelium remained intact blanched within twenty-four to forty-eight hours after the administration of the drug. However, severe cases of dermatitis in which the lesions were moist, ulcerated, and thickened did not seem to benefit by nicotinic acid. In several cases there was flushing of the dermal lesions with tingling of the skin shortly after the administration of the drug. These authors conclude that 0.5 gramme daily, in five doses of 100 mg. each, is a safe and effective amount in the usual case of pellagra.

In a further report Spies (1938) describes fifteen cases similarly studied and treated. In these the urine was tested for porphyrin. In one case the porphyrin disappeared from the urine forty-eight hours after the beginning of treatment, only to reappear when the nicotinic acid was discontinued. In a later communication Grant, Zschiesche, and Spies (1938) again confirmed these observations, and pointed out that the healing of the dermatitis was completed by the end of the second week.

Smith, Ruffin, and Smith (1937) report a chronic case of pellagra with typical dermatitis, hyperkeratosis of the face, diarrhoea, and mild dementia which responded to nicotinic acid. Yudkin, Hawksley, and Drummond (1938) report a case which was successfully treated with a "liver filtrate" factor. In a later communication Hawksley (1938) records a case ending in recovery after treatment with nicotinic acid. He concludes that the liver filtrate factor used in the previously treated case must contain nicotinic acid.

We shall briefly describe two cases of pellagra which were successfully treated with nicotinic acid.

Case I

A woman aged 62 was admitted to hospital on April 12, 1938, having previously been observed for eight days in the out-patient department. Four months before admission she began to complain of severe diarrhoea consisting of four to six foul liquid stools daily. The diarrhoea persisted in spite of medication. The patient then put herself on a diet of white bread, crackers, zwieback, rice, milled cereal, white cheese, and black coffee. Sugar, meat, vegetables, fish, butter, eggs, and milk were rigidly excluded from the diet. The patient felt weak and listless, and lost considerable weight. The diarrhoea persisted. One month before admission she noticed that the skin on the dorsum of the hands was rough and scaly. The lesion progressed rapidly until the dorsum of the hands became fiery red and scaly. At the same time she noticed red circles under the eyes, somewhat similar to the skin of the hands. One week before admission she began to complain of burning of the tip of the tongue.

Physical Examination.—The patient was well orientated and co-operative. She appeared chronically ill and undernourished. The skin of the face was dry, atrophied, and wrinkled. Under the eyes it was reddened, rough, and scaly. Around the neck there was a wide band of brown pigmentation. The dorsum of the hands was wrinkled, fiery red, and covered with a scaly dermatitis extending from the nail-beds to the wrist. There were areas of deep brown pigmenta-

tion at the wrists and the carpo-metacarpal articulations. There was a moderate pigmentation on the dorsum of the feet. The tongue showed some atrophy of the papillae at the margin, with reddening of the tip. The patellar and Achilles reflexes were somewhat hyperactive, but no abnormal reflexes were present. Vibratory sense was diminished to the knees, as was perception of touch, the patient being unable to distinguish between the head and point of a pin. There was no pain on pressure on the leg muscles. The Romberg sign was absent. Motor power appeared normal. The rest of the examination produced nothing abnormal.

Laboratory Data.—The stool contained no parasites or ova. The urine was normal. The red cells numbered 3,900,000 per c.mm. and the haemoglobin amounted to 75 per cent. Sahli. The white cells totalled 7,200 per c.mm., and the differential count was normal. Radiographs of the stomach and duodenum revealed nothing of note. The gastric juice showed complete achlorhydria.

Clinical Course.—The patient was put on a basic diet similar to that of Spies, sufficient in protein, fat, and carbohydrates, but deficient in the pellagra-preventive factor. The dermatitis and diarrhoea became more marked, weight loss was rapid, and the appetite continued poor. On the fourth day after admission, while continuing the basic diet, she was given two 50 mg. doses of nicotinic acid by mouth. The amount was then increased to 150 mg. daily, given orally in three 50 mg. doses, until discharge from the hospital. On the second day of the treatment there was a slight improvement in the dermatitis with desquamation starting in the central portion of the dermal lesions of the hands. The tongue was no longer reddened, and the marginal papillae appeared normal. The appetite improved considerably. On the fourth day of treatment the diarrhoea suddenly ceased, and throughout her stay in hospital the patient had one normal stool daily. Five days after the beginning of treatment she complained of tingling of the finger-tips, flushing of the face, and dizziness. The drug was discontinued for two doses, but on the sixth day was continued without untoward effect.

By the sixth day of treatment the dermatitis of the hands had disappeared except for a small area of pigmentation at the wrists. By the tenth day the skin was entirely normal. Since the results of the nicotinic acid had been so striking, eggs, milk, purée of vegetables, and chicken were added to the basic diet. Her only complaint was weakness of the legs and some difficulty in walking. The results of neurological examination made at this time were the same as on admission, except that vibratory sense was now normal. Because of these symptoms, from the fourteenth day the patient was given one ampoule of crystalline vitamin B_1 (betaxin) intramuscularly daily, until discharged nine days later. At discharge the reflexes were still hyperactive, but sensation was completely normal. She no longer complained of difficulty in walking or weakness in the legs. Her weight, in spite of the pronounced general improvement, remained constant (44 kg.). However, this woman was seen in the out-patient department ten days later, and had gained 3 kg. in weight with no treatment other than a normal mixed diet.

Case II

The patient, a porter aged 46, was first seen in the out-patient department ten days before admission to hospital. When admitted on April 28, 1938, it was impossible to obtain a detailed history from him because of his obvious mental confusion, depression, and anxiety. However, a history was elicited at a later period of his illness, when his mental condition had greatly improved. He had been unemployed for five months, and during this interval his diet had consisted entirely of unleavened bread, rice, potatoes, lentils, and occasional cabbage or boiled egg-plant. His appetite had become very poor. For three months he had felt extremely weak, could no longer lift heavy objects, and finally could hardly walk. He complained of dizziness and dull aching pains over the entire body. One month before admission he first noticed that his hands were becoming fiery red and painful. This he attributed to constant exposure to the sun. He did not complain of diarrhoea or a sore mouth.

Physical Examination.—The patient was uncooperative, disorientated, and appeared badly nourished and severely ill. His face looked apathetic and listless. The dorsum of the hands was covered with thick scaly hyperkeratotic fiery red dermatitis, deeply fissured and ulcerated. In some areas there were blotches and brown pigmentation. The feet showed a similar but less severe dermatitis. The orifices of the sebaceous glands about the nose were plugged with horny concretions. The tongue was coated, no glossitis or papillary atrophy being present. The heart sounds were distant and of a tick-tack quality. Neurological examination revealed absent patellar and Achilles reflexes. The abdominal reflexes were present. Sensory examination was impossible because of the confused mental condition of the patient. The gait was ataxic and swaying, with small steps. The Romberg sign was absent. The rest of the examination was not notable.

Laboratory Data.—The urine was normal, but porphyrin was present on admission. There were 3,000,000 red cells per c.mm. when admitted and 4,100,000 on discharge; the haemoglobin was 60 per cent. Sahli, and the differential count was normal. The Wassermann reaction was negative. The stools contained no parasites or ova. The gastric juice showed complete achlorhydria. A radiograph of the stomach revealed severe gastritis with thickening of the rugae. A radiograph of the heart did not show any enlargement.

Clinical Course.—The patient was put on a basic diet similar to that of Case I. His appetite was poor and he refused most of his food. He was uncooperative and disorientated, and urinated on the floor of the ward. On the day of admission treatment was begun with 50 mg. of nicotinic acid. The next day he was given two doses of 50 mg. each. After the second dose the patient complained of severe itching over the areas of dermatitis, flushing of the face, and faintness. An urticarial rash appeared over the knees, back, and arms; this persisted for two hours. The drug was discontinued for the third and fourth days. Meanwhile his dermatitis and mental state became distinctly worse. On the fifth day he was given two doses of 10 mg. each, on the sixth day 10 mg. eight times, on the seventh day 50 mg. three times, and subsequently 50 mg. four times daily until discharge. No further reactions to the drug were observed. On the seventh day, after a total dose of 400 mg. of the drug, the dermatitis showed marked improvement. The appetite was very good, but the mental condition had not improved. By the twelfth day of treatment the dermatitis of the hands had completely disappeared except for a small area of pigmentation at the wrists. The skin of the nose was now entirely normal. The patient's mental condition had shown marked improvement, and he was now rational and co-operative, and walked about the ward. In spite of his basic diet he had gained 1.8 kg. in weight. By the thirteenth day of treatment he was completely normal mentally, and his appetite could no longer be satisfied by the pellagra-producing diet. He was therefore given a regular diet on the fourteenth day. Neurological examination still revealed absent knee and Achilles reflexes, but the sensory examination appeared normal. The patient was now exposed to the direct sunlight for periods of one and a half hours on several occasions. The dermatitis did not recur. On the eighteenth day the urine, in which porphyrin was found on admission and on the eighth day in hospital, no longer contained this substance. On discharge on the twenty-third day he was in excellent health and had gained 3 kg. in weight.

Summary

Two cases of pellagra are reported in which the patients, while subsisting on a basic pellagra-producing diet, were treated with nicotinic acid. Both patients recovered from the disease, the first by the ninth, and the second by the thirteenth day of treatment. The average dose varied from 150 to 200 mg. orally a day. Both patients had

reactions to the drug early in the treatment. In Case II the mental symptoms disappeared with treatment.

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Clinical Memoranda

Basal Narcosis in the Treatment of Tetanus

Recovery from generalized tetanus of short incubation period is rare enough to justify presentation of this case. The remarkably beneficial effects of continuous and intermittent basal narcosis (in this particular patient with nembutal) would seem to suggest that this form of treatment is a most valuable means of combating a dread disease.

CASE REPORT

A man aged 28, of robust build, was admitted to St. Vincent's Hospital, Dublin, on March 24, 1938, presenting the classical signs and symptoms of established generalized tetanus; temperature 101° F., pulse 102, respirations 30. The patient, who was fully conscious, stated that he had been in perfect health until March 19, when he developed cramps in his legs and pain and stiffness in his jaw and neck, which subsequently spread to all parts of his body. He remembered having cut his forearm with a shovel on March 12 while handling animal offal in a factory. He did not pay any attention to the cut except to apply iodine. As the nature of his illness had not been recognized locally no anti-tetanic serum had been given before his admission to hospital.

Treatment.—The wound in the forearm, which was septic, was freely incised and treated with hydrogen peroxide. For the first three days in hospital continuous narcosis was maintained with 7½ grains of nembutal, given intravenously at chosen intervals, and during this time continuous intravenous drip glucose saline was administered (10 pints). From the fourth day onwards the nembutal was given by mouth in 4½-grain doses so as to produce intermittent narcosis, which allowed the patient to have adequate nourishment, aperients, and plenty of fluids during the day-time. As the patient was rather restless on the fifth day two intravenous injections of the drug were necessary. Extending over a ten-day period a total dosage of 75 grains of nembutal was given by the intravenous route, and of 63 grains by the oral route. During the same ten-day period 240,000 units of anti-tetanic serum were administered: 6,000 units intravenously (under chloroform anaesthesia), 20,000 intravenously, and the remainder by the intramuscular route.

Progress.—All tetanic spasms had ceased by March 28, temperature and pulse were normal on March 30, but residual stiffness did not show signs of passing off until the tenth day of treatment. After this the patient made an uninterrupted recovery.

Notwithstanding the large quantity of anti-tetanic serum administered in this case the clinical behaviour of the patient was such as to suggest that the outstanding beneficial agent was the prolonged narcosis produced by the nembutal in conjunction with the intravenous drip therapy.

The use of basal narcotics in the treatment of tetanus is of course by no means new. Avertin was employed for this purpose by Läwen as far back as 1927, since when there have been frequent references in the literature to the use of various narcotic drugs—chiefly barbiturates. This present case is placed on record with a view to emphasizing the value of a method of treatment which is easily applied and which offers a considerable prospect of a successful outcome.

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Stable Sodium Nitroprusside Solution for Acetone Bodies in Urine

Most of the tests for acetone bodies in the urine are performed by dissolving, just before use, a few crystals of sodium nitroprusside in 5 c.cm. of water and adding a few drops of this solution to the urine, containing ammonium sulphate and floating on ammonia. This aqueous solution of sodium nitroprusside is very unstable, turning blue when kept for a few hours, so that for practical purposes it has to be freshly prepared every day. Unless a large number of urines have to be tested daily much of the sodium nitroprusside is wasted. When only one or two urines have to be examined some workers simply place a few crystals—approximately 0.2 gramme—of sodium nitroprusside and a small quantity—about 3 grammes—of ammonium sulphate in a test tube, then add about 5 c.cm. of the urine direct to the mixed salts and float the ammonia on the top. This procedure is also very wasteful of sodium nitroprusside.

Sodium nitroprusside is an expensive chemical—over 26s. per 500 grammes—and a stable solution would therefore not only be much more convenient for urine testing but would also help to reduce the running costs of the laboratory. An aqueous solution of sodium nitroprusside can be rendered quite stable, however, merely by the addition of a little concentrated nitric acid, which in no way interferes with the reaction for acetone bodies in the urine. This solution will keep indefinitely, and so is always ready for use. With regard to the ammonium sulphate used in the test, it is also more convenient to keep it as a mixed solution with ammonium hydroxide.

The reagents for the improved test therefore would be:

Solution No. I.—Ammonium sulphate solution:
200 c.cm. saturated solution of ammonium sulphate,
200 c.cm. ammonium hydroxide, sp. gr. 0.88.

Solution No. II.—Sodium nitroprusside solution:
10 grammes sodium nitroprusside crystals dissolved in
90 c.cm. distilled water, and
1 c.cm. concentrated nitric acid then added.

The Test.—To 5 c.cm. of urine in a test tube add 5 c.cm. of solution No. I and mix. Then add 1 c.cm. of solution No. II, shake, and allow to stand for a minute before judging the colour reaction. A deep purple colour will then have appeared if 0.1 per cent. or more of acetone bodies is present. If only a very faint trace is present the colour will be merely deep red.

The saturated solution of ammonium sulphate used in solution No. I should be prepared as follows: Place 780 grammes of ammonium sulphate in a 2-litre flask and add 1 litre of boiling distilled water. Shake immediately until dissolved, then allow to cool at room temperature. Decant the supernatant solution (or filter if necessary).

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