resembled pemphigus. These symptoms and the fever persisted (Fig. 2) until the phenindione was discontinued 11 days later. He made an uneventful recovery and left hospital seven weeks after admission. Ten days later anginal pain recurred, and his general practitioner gave him phenindione 50 mg. b.d. Fever and generalized aching in the muscles and eyes returned, and he was readmitted two days later. There was no clinical or E.C.G. sign of further infarction. Culture of blood, sputum, and urine again revealed no pathogens. The W.B.C. numbered 6,800/c.mm., with a normal differential count. The anticoagulant was stopped and the fever subsided rapidly. The patient made an uneventful recovery.

Case 3.—An 82-year-old woman was admitted to hospital on account of severe retrosternal pain, which was shown to be due to cardiac infarction. She was treated with phenindione, and a satisfactory control of the prothrombin level was achieved. After three weeks she developed a fever up to 101.8° F. (38.8° C.) for which no cause could be found. The white-cell count was normal. After a week of fever the anticoagulant was stopped, with immediate remission of the fever. She made an uneventful recovery.

Case 4.—A man of 67 was admitted to hospital on account of central chest pain which was shown to be due to a cardiac infarct. He was treated with phenindione, but he developed a fever on the 19th day. This persisted, and was accompanied by numerous mouth ulcers and a disproportionate tachycardia. After 14 days of fever he was seen by one of us and was thought to be suffering from a drug fever. His fever abated promptly when the phenindione was stopped. The mouth ulcers healed rapidly with the help of hydrocortisone lozenges, and he recovered.

Case 5.—A 69-year-old man who had previously been healthy suddenly became breathless and faint while walking home from a dinner. Three days later he had left-sided pleuritic pain. These symptoms persisted and he developed fever up to 102.6° F. (39.2° C.). He was admitted to hospital on October 4, 1956, a fortnight after the onset. Clinical and radiographic signs of a pulmonary infarct were found. He was treated with phenindione and penicillin; the fever, pain, and dyspnoea gradually disappeared. The penicillin was discontinued after 10 days. After three weeks in hospital he became febrile, the temperature rising to 104° F. (40° C.). On October 28 his white cells numbered only 3,000, with 8% neutrophils. Blood and urine cultures were sterile, and the Widal test was negative. On November 6 he developed a pharyngitis, and the next day his white-cell count was down to 2,800/c.mm., with 7% neutrophils. Further bacteriological examinations were negative, but he was treated with penicillin 250,000 units six-hourly. On November 9 the anticoagulant was discontinued, and the temperature quickly returned to normal. The penicillin was continued, and in addition cortisone 25 mg. daily was given because of the agranulocytosis. There was a prompt rise in the white-cell count, with healing of the mouth and pharynx. He was discharged on November 29 quite fit, and subsequent blood examinations were normal.

Case 6.—A man aged 55 developed substernal pain which was shown by E.C.G. to be due to a cardiac infarct. He was treated at home with phenindione and stabilized on a dose of 100 mg. daily. Twenty-three days after the start of the anticoagulant he developed ulcers in the mouth, a generalized urticarial eruption, and a temperature of 101° F. (38.3° C.). The white-cell count was normal. All the symptoms subsided within two days of stopping the phenindione, and he made an uneventful recovery.

Comment

Febrile reactions may occur occasionally to most drugs, and it is therefore not surprising to find such reactions to phenindione. Febrile reactions to phenindione have so far been reported in 13 patients (Bingle and Shine, 1959). We are drawing attention to this idiosyncrasy as early recognition may prompt the physician to withdraw the drug and prevent more serious complications. It is possible that neutropenia in Case 5 could have been avoided if the fever had been attributed to a drug reaction at an earlier date. Only one fatal case of agranulocytosis due to phenindione treatment has so far been reported (MacMillan and Brown, 1953). Thus both febrile and neutropenic reactions must be an extreme rarity considering the large scale on which the drug is used. Our experience with these reactions has not altered our opinion that phenindione is in general a safe and reliable anticoagulant.

Summary

Six examples are reported of drug fever occurring during phenindione ("dindevan") treatment. In one of them profound neutropenia developed, but the patient recovered.

We thank Dr. R. Kemball Price and Dr. C. Barrington Prowse for permission to refer to patients under their care.

REFERENCES

Bingle, J., and Shine, I. (1959). *Lancet*, **2**, 377.
MacMillan, R. L., and Brown, K. W. G. (1953). *Canad. med. Ass. J.*, **69**, 330.

DANGEROUS POTENTIATION OF PETHIDINE BY IPRONIAZID, AND ITS TREATMENT

BY

J. CHARLES SHEE, M.D., M.R.C.P., D.T.M.&H.
Honorary Consultant Physician, Bulawayo General Hospital, Bulawayo, S. Rhodesia

Iproniazid, a close chemical relation of isoniazid, was first introduced for its antituberculous action. It was noted to have a euphoriant effect, and for this reason has been used in psychiatry, in the treatment of depressive states. This antidepressive effect is possibly due to its being an inhibitor of mono-amine oxidase. It has recently become popular in cardiology, for use in cases of intractable angina pectoris (Cossio, 1958; Towers and Wood, 1958).

Mitchell (1955) reported the case of a patient, receiving treatment for tuberculosis with iproniazid, who developed nausea and muscle twitching 20 minutes after being given 100 mg. of pethidine. He became cyanosed, was sweating, and had a rapid pulse, exaggerated tendon reflexes, ankle clonus, and a bilateral extensor plantar reflex. The attack subsided within 36 hours. Papp and Benaim (1958) described the case of a woman receiving iproniazid, 50 mg. t.d.s., for decubital angina. She had a severe attack of pain, not relieved by the injection of pethidine, 100 mg.; this was repeated after half an hour, and within minutes the woman had passed into a state of semiconsciousness with uncontrollable hyperactivity, and became completely unmanageable. Paraldehyde, 5 ml., various barbiturates, and promethazine, 50 mg. by injection, were given without effect. Finally, chlorpromazine, 50 mg. by injection two hours after the attack started, quieted her. The iproniazid was stopped. The next day, when she had a further bout of angina, suppressed by 200 mg. of pethidine, a similar state recurred, easily controlled by an injection of 50 mg. of chlorpromazine.

Two days later a further attack of pain was controlled by 200 mg. of pethidine and was not followed by restlessness.

The purpose of this paper is to describe two further cases which, on a similar combination of drugs, developed reactions even more frightening and dramatic than the two referred to above; in both cases the reversal of the syndrome by the intravenous injection of prednisolone was rapid.

Case 1

An obese woman aged 58 sustained a coronary thrombosis in July, 1958. Since recovery she had suffered from angina pectoris, which at times attained the severity of angina decubitus. In October, 1959, she was seen by a physician, who prescribed 50 mg. of iproniazid b.d. She did not obtain much relief, and as the drug caused dizziness, dysuria, and insomnia she stopped taking it of her own accord, the last dose being taken on the morning of the day before the incident reported here. On the evening in question she complained of acute precordial pain, and, her usual doctor not being available, another one, who had not known her previously, was called in at 11 p.m. He diagnosed angina decubitus, and gave her 100 mg. of pethidine intramuscularly. She became restless and incoherent almost immediately, and within 20 minutes was in coma. She was taken to hospital at once.

On examination in hospital within an hour of receiving the injection, she was flushed, was sweating profusely, and was in deep unrousable coma; she had Cheyne–Stokes respiration, with apnoeic pauses lasting as long as 10 seconds, both eyes were deviated upwards, and the pupils were widely dilated and unreactive. Deep reflexes could not be elicited, and both plantar reflexes were extensor. Her pulse rate was 82 a minute and the B.P. 156/110. The picture suggested a major intracranial vascular disaster, but, with the possibility of an acute drug-reaction in mind, 25 mg. of prednisolone hemisuccinate was injected intravenously. Within a few minutes there was a lightening of the level of consciousness, she was responding to painful stimuli, and in 10 minutes she was rousable.

No further treatment was given, and she slept through the night. Next morning she felt quite well, her B.P. was 162/106, and an E.C.G. showed ischaemic changes consistent with an old posterior cardiac infarction. She was discharged from hospital that day without further mishap.

Case 2

A man aged 64, known to have been hypertensive, had suffered from angina pectoris for about 10 years. In 1956 he was found to have a gastric ulcer. In 1957 he suffered a major anterior cardiac infarction, from which he made a good recovery. He continued to have angina, which became very severe towards the end of 1958, and in February, 1959, he was put on iproniazid, 50 mg. b.d. He thought this reduced the severity and frequency of his attacks, and from May he took 50 mg. every morning; he also took reserpine, 0.25 mg. t.d.s., and occasionally nitroglycerin, with caution, as it tended to precipitate episodes of glaucoma. On April 7, 1960, he was admitted to hospital at 12 noon for a haematemesis which had begun about 12 hours previously. Before admission he was given ¼ gr. (15 mg.) of morphine at 7 a.m., and again at 9 a.m., without any adverse reaction.

On admission he was pale and collapsed, his blood pressure was 110/90, pulse rate 116, and haemoglobin 8.6 g./100 ml. An initial dextrose–saline intravenous infusion was set up and a blood transfusion was started at 1.45 p.m. As he was still restless and complained of anginal pain, 100 mg. of pethidine was ordered, being injected at 2 p.m.

Almost immediately he became restless, twice became convulsed, and when seen 20 minutes after the injection was deeply comatose, the clinical picture being almost identical with that of Case 1, including bilateral extensor plantar responses, vertical deviation of the eyeballs, absence of deep reflexes, and Cheyne–Stokes respiration. His blood pressure was now 142/90 and pulse rate 90, although he had received only 300 ml. of dextrose-saline and perhaps 100 ml. of blood since treatment began.

It was known that his last dose of iproniazid had been taken at 9 a.m. on the previous day. With Case 1 in mind, he was given 25 mg. of prednisolone hemisuccinate intravenously via the transfusion tubing at 2.30 p.m., and there was the same almost immediate response. Within five minutes he was rousable. He slept without restlessness through the afternoon, and at 6 p.m. his level of consciousness was normal. There were no apparent bad after-effects.

A range of empirical liver-function tests three days after the attack was quite normal.

It was later shown that the haematemesis was due to a gastric ulcer.

Discussion

The most serious toxic effect of iproniazid described is jaundice (Kline, 1958).

Benaim and Dixon (1958) recorded two cases of jaundice occurring during a clinical trial of iproniazid in 60 depressed patients. A liver biopsy in their first case suggests that iproniazid is a hepatotoxic drug; in the second case liver biopsy was inconclusive, and as the patient had also received chlorpromazine, a known hepatotoxic drug, no further conclusion can be drawn. A fatal case of acute hepatic necrosis has been reported by de Verteuil and Lehmann (1958).

Minor toxic effects reported include muscle tremor, increased reflexes, constipation, dysuria, insomnia, dizziness, headache, orthostatic hypotension, peripheral neuritis, psychosis, and intensification of pre-existing epilepsy (Dewar, Horler, and Newell, 1959).

The toxic effects of pethidine include dizziness, sweating, dry mouth, and vomiting; overdosage leads to incoordinate tremors, convulsive movements, and tachycardia; and severe cases show respiratory depression and coma. As the drug is detoxicated in the liver, care is needed in its use in patients with hepatic dysfunction, and the therapeutic effect is obtained with smaller dosage (Dundee and Tinckler, 1952).

A recent case of pethidine idiosyncrasy that I encountered showed quite a different picture from that of the two cases described here. The patient was pale rather than flushed; he was restless and semiconscious, with a rapid pulse and low blood-pressure; and he appeared to be in peripheral heart-failure. His circulatory collapse responded gradually to intravenous nalorphine and hydrocortisone hemisuccinate. It is emphasized that the two cases of pethidine–iproniazid coma described here, although both had severe ischaemic heart disease, showed no evidence of circulatory distress during the reaction.

This reaction appears to be a more advanced stage of that described by Papp and Benaim (1958), whose patient was restless and uncontrollable, but not in coma; the restlessness in their case was readily controlled by chlorpromazine. It seems unlikely that the reaction is mediated through liver damage, as their case, and one of the cases described here, had normal liver-function tests.

A possible mode of action is that when pethidine encounters iproniazid or its degradation products in sufficient quantity in the body it forms a loose chemical combination which initially causes cerebral irritation and, in higher concentration, coma; and that this chemical combination is specifically blocked or reversed by prednisolone.

After initial enthusiasm, two adverse reports on the efficacy of iproniazid in angina pectoris have appeared (Dewar *et al.*, 1959; Snow and Anderson, 1959). Both papers were based on controlled "double-blind" clinical trials. It seems unlikely that the drug will benefit many patients with angina pectoris.

Angina patients are particularly liable to develop cardiac infarction and to be admitted to hospital under the care of physicians not fully acquainted with their previous medical histories, and may be given pethidine for the relief of their pain. It is suggested, in the light of the two cases reported here and that reported by Papp and Benaim, that iproniazid be reserved for the most intractable cases of angina, and be given only where all other measures have failed. If a patient on iproniazid has to be admitted to hospital for any reason, his introductory letter should state, "No pethidine, please."

Summary

Two cases are described in which patients receiving iproniazid for angina pectoris were precipitated into rapid and deep coma by the injection of pethidine.

In each case intravenous prednisolone appeared to cause immediate and specific reversal of the reaction.

REFERENCES

Benaim, S., and Dixon, M. F. (1958). *Brit. med. J.*, **2**, 1068.
Cossio, P. (1958). *Amer. Heart J.*, **56**, 113.
de Verteuil, R. L., and Lehmann, H. E. (1958). *Canad. med. Ass. J.*, **78**, 131.
Dewar, H. A., Horler, A. R., and Newell, D. J. (1959). *Brit. Heart J.*, **21**, 315.
Dundee, J. W., and Tinckler, L. F. (1952). *Brit. med. J.*, **2**, 703.
Kline, N. S. (1958). *J. clin. exp. Psychopath.*, **19**, Suppl. 1, p. 72.
Mitchell, R. S. (1955). *Ann. intern. Med.*, **42**, 417.
Papp, C., and Benaim, S. (1958). *Brit. med. J.*, **2**, 1070.
Snow, P. J. D., and Anderson, D. E. (1959). *Brit. Heart J.*, **21**, 323.
Towers, M. K., and Wood, P. (1958). *Brit. med. J.*, **2**, 1067.

EFFECT OF PHYSICAL EXERCISE ON ALIMENTARY LIPAEMIA

BY

HAROLD COHEN, M.B., M.R.C.P.
Senior Registrar, Royal Hospital, Sheffield

AND

CISSIE GOLDBERG, B.Sc.
Statistician

The increase in turbidity of blood plasma after a fatty meal is a familiar observation. Its duration and intensity are of particular interest, because it has been shown that patients with coronary artery disease, taken as a group, exhibit delayed clearing of this visible lipaemia (Becker, Meyer, and Necheles, 1949; Schwartz, Woldow, and Dunsmore, 1952; Barritt, 1956). The mechanism by which this abnormality is related to coronary artery disease is unknown. As there is good evidence that the physical activity of work is a protection against coronary (ischaemic) heart disease (Morris and Crawford, 1958), we have studied the effect of exercise on the clearing of alimentary lipaemia, and the results of our observations are presented in this article.

Methods

Twenty-two healthy medical students, whose ages ranged from 20 to 25 years, volunteered for the tests. In the whole group there were 12 men and 10 women.

The subjects, having fasted overnight, were given one of the following standard breakfasts: *75-g. fat breakfast:* ½ oz. (14 g.) cornflakes, 1 oz. (28 g.) medium fat fried bacon, one fried egg, 2 oz. (57 ml.) cream, 3 oz. (85 ml.) milk, 1 oz. (28 g.) butter; *60-g. fat breakfast:* ½ oz. (14 g.) cornflakes, two boiled eggs, ¾ oz. (21 g.) butter; 2 oz. (57 ml.) cream, 4 oz. (114 ml.) milk. No restriction was placed on the amount of bread, tea or coffee, and marmalade which could be taken, but the students were asked to eat the same amount at each of the test meals.

The principle of the investigation was to measure plasma turbidity at a given time after the standard meal with the subject resting, then to repeat the test under similar conditions except that the subject did a standard amount of physical exercise; thus each individual acted as his own control.

The first six students who volunteered (group 1, see Table) were divided into two parties. After the first standard meal one party rested while the other exercised, and 10 days later, when the observations were repeated, the parties changed round, those who had previously rested taking exercise, and vice versa. This group took breakfast (75 g. fat) at 9 a.m., then either rested for the remainder of the test, spending most of their time sitting and reading, or took exercise. For exercise they walked 4 miles (6.4 km.) from 10.15 to 11.45 a.m. and 2 miles (3.2 km.) from 12.30 to 1.30 p.m., then rested for the final two and a half hours of the test. They were allowed a drink of clear fluid at 1.30 p.m. Care was taken to ensure that the conditions of each test were similar. The students smoked the same number of cigarettes on each occasion and drank the same type and amount of fluid.

Blood samples were taken into oxalate tubes before breakfast and at three, five, and seven hours after the start of the meal. The plasma was separated and the turbidity measured in a Unicam spectrophotometer at 6,700 Å.

Similar observations were made on another group of 14 students (group 2). These were given a 60-g. fat breakfast, after which they rested for three hours before taking exercise. They then walked 6 miles (9.6 km.) in two to three hours. During the test they were allowed only water to drink. One blood sample was taken, at six hours after the start of the meal; the plasma was separated and the turbidity measured.

The effect of short bursts of more strenuous exercise was tested. Two students (group 3) ate a 75-g. fat breakfast and then rested for three hours. In the subsequent four hours they cycled on a stationary machine for two periods of half an hour. In each period the cycling was equivalent to 5 miles (8 km.) up a slight incline.

Results

The results for group 1 taken as a whole are shown in Fig. 1. In four of the six students the plasma turbidity was lower throughout the test when exercise was taken after the meal than when they rested. The plasma of one student (Subject 1) was more turbid when she exercised than when she rested. In this case the plasma turbidity remained very low throughout the test on the occasion that she rested, and absorption of fat may have been affected by an alimentary disturbance. Nevertheless, these results have been included. Another student (Subject 3) had decreased plasma turbidity at three and five hours after exercise, but not at seven hours. In general the intensity of lipaemia after a fatty meal was