tory investigations showed an increase in gamma-globulin, a decreased pseudo-cholinesterase, and increased bromsulphthalein retention in the absence of a rise in serum bilirubin. These findings were suggestive of hepatic dysfunction.

Pare (personal communication) has studied the effect of iproniazid on the serum transaminase level and found this to be increased in some patients, although other liver-function tests remained normal. This again might suggest some liver dysfunction.

Further evidence of liver involvement is supplied by Fouts and Brodie (1956). These authors discovered that iproniazid inhibited the enzymes in the liver, whose function is to detoxify such drugs as barbiturates, amphetamine, aminopyrine, and acetanilid. Toxic cerebral reactions following injections of pethidine have been reported by Mitchell (1955) and by Papp and Benaim (1958), and can be similarly explained on the basis of potentiation of the drug by iproniazid.

Randall (1958) reports slight parenchymatous degeneration in the liver and kidney, engorgement of the spleen, and bone-marrow hyperplasia in animals receiving large doses of iproniazid. Such changes were dependent on the dosage administered, and all were reversible.

Our two cases of jaundice occurred during a clinical trial of iproniazid on 60 depressed patients. Case 1 had received the drug for 72 days to a total of 8.6 g. when jaundice developed. The course of the disease was unlike that of infective hepatitis. Prodromal symptoms were minimal, asthenia and anorexia becoming marked only when clinical signs of necrosis supervened. Liver enlargement and tenderness were slight. There was no fever, and the E.S.R. remained normal throughout her illness. The initial liver-function tests were in favour of intrahepatic cholestasis. In common with other investigators, we found disturbance of protein metabolism with an increase in globulin. Unfortunately, electrophoretic studies were not carried out. The marked change in condition on the twelfth day of jaundice, with the development of clinical signs of liver failure, pointed to the onset of necrosis. This diagnosis was supported by a high serum transaminase level and by the biopsy findings, which showed evidence of focal necrosis in spite of the administration of corticotrophin for three days beforehand. Moreover, the presence of eosinophilia in the sections is strong evidence of drug-induced jaundice (Hollister, 1957).

Case 2 had received iproniazid for 75 days to a total of 11.25 g. It is unfortunate that the case was not seen until 22 days after the onset of jaundice, by which time she was recovering. No definite conclusions can be reached on the information available.

The hypothesis was originally put forward that jaundice occurring in iproniazid therapy was due to a coincidental occurrence of viral hepatitis and an inhibition of the amine oxidase system by the drug, causing failure of the detoxicating mechanisms of the liver. From the evidence available, however, it is difficult to escape the conclusion that iproniazid may have a direct toxic effect on the liver. The fact that jaundice has occurred in patients receiving as little as 25 mg. daily and that it appears unrelated to the duration of administration (Marks, personal communication) suggests that an element of idiosyncrasy may be present.

While it is difficult to decide at this stage whether iproniazid jaundice is of obstructive or hepatocellular type, the severity of some of the cases reported, including our first case, supports the latter possibility. Moreover, our liver biopsy provided definite evidence of hepatocellular damage. The picture was very different from that encountered in chlorpromazine jaundice, obstructive in type and benign in course, in which one invariably finds bile plugs in biliary canaliculi and minimal inflammatory changes (Movitt *et al.*, 1955).

It is clear that further research is needed to establish beyond doubt the mechanisms whereby iproniazid produces liver damage and jaundice. It is hoped that such risks can be eliminated and that this very helpful drug can continue to be used by psychiatrists and physicians with a greater degree of safety.

Summary

Two cases of jaundice occurring during a clinical trial of iproniazid in 60 depressed patients are reported. Both patients recovered.

Details of biochemical investigations and of a liver biopsy are given. These, together with the course of the disease, suggest that iproniazid is a hepatotoxic drug. Possible mechanisms of action are discussed and the need for further research is emphasized.

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TOXIC EFFECTS OF IPRONIAZID IN A PATIENT WITH ANGINA

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Iproniazid (" marsilid "), closely resembling isoniazid in its chemical structure, was originally planned as an antituberculosis drug. Its use in tuberculosis had to be abandoned because of its unpredictable side-effects on mood, ranging from mental excitement to frank psychoses, when given in doses of 4 mg. per kg. of body weight (200–300 mg. a day) as at first advised (O'Connor, Howlett, and Wagner, 1953). This euphoric effect was recently exploited in psychiatry for the treatment of mental depression, where, with smaller doses (100–150 mg. a day), promising results were obtained (Kline, 1958; Dally, 1958). The use of iproniazid in angina pectoris is based on a chance observation in a patient with mental depression who recovered from incapacitating angina while on the drug. Encouraged by this result, Cesarman (1958) tried iproniazid in 41 patients with moderate to severe angina. He reports " total remission " of anginal pain in all of his patients, with electrocardiographic improvement in some. Cossio (1958) out

of 36 patients found almost complete relief of angina in 15, improvement in 11, and no benefit in 10. The daily dose varied from 100 to 150 mg. (two to three tablets). Side-effects have been minor, such as euphoria, constipation, difficulty of micturition, giddiness caused by orthostatic hypotension, and impotence. Dally in his recent large series of 131 psychiatric patients mentions only two in whom treatment had to be stopped on account of fainting caused by postural hypotension.

We were less fortunate in one patient, out of the few, in whom the drug was given for incapacitating decubital angina by one of us (C. P.). This patient developed a transitory toxic cerebral state while taking iproniazid.

Case Report

A married woman underwent bilateral lumbo-dorsal sympathectomy for severe hereditary hypertension in 1948, when aged 40. There was at the time slight renal involvement and grade II–III retinopathy; but the main indication for operation was disabling angina with attacks refractory to nitrites, lasting for hours, cut short only by injections of morphine. She did not sustain cardiac infarction then or at any time later, and the electrocardiogram showed extreme left ventricular strain with ischaemic changes only. Surgery proved a great success; she was able to resume an active life, lost the angina, and the electrocardiogram reverted to normal. Now, ten years after the operation, the blood pressure in erect posture is still normal, while in recumbency it varies between 160/100 and 180/120.

During the past four years the cardiac symptoms recurred in the form of increasingly severe decubital angina. It was thought that the raised blood pressure in the lying position was causing the attacks, during which the electrocardiogram showed acute ischaemic changes. Prolonged bed rest with ganglion-blocking agents and rauwolfia, which effectively lowered the recumbent blood pressure, did not prevent the attacks. Heavy sedation, long-acting nitrites, and various coronary vasodilators were all tried without success. Parenteral pethidine, 100 mg. at first, later 200 mg., suppressed attacks of moderate severity; occasionally she needed morphine in addition. Pethidine never caused any side-effects, and the morning after the injections she was as usual active in her home. In March, 1958, when she had almost daily attacks, left stellate ganglionectomy was performed. After a fortnight the attacks reappeared and within days they became as severe as they were before the operation.

Iproniazid was started on April 26. For the first fortnight she was given 50 mg. twice a day, then three times a day. After a fortnight the attacks became less frequent—about twice weekly, and milder. Trinitrine was effective for the lighter attacks, though for the severe ones she still required pethidine injections. At this stage the only adverse iproniazid effect was pronounced postural hypotension. On May 27 she complained of difficulty of micturition. At 10 p.m. on May 30, after not having had angina for four days, she had a severe attack. Pethidine, 100 mg. by injection, did not relieve her, and the same dose was repeated half an hour later. Within minutes she became extremely restless and confused, and passed into a state of uncontrollable hyperactivity. She was tossing and turning, flopping her arms aimlessly, and it was difficult to keep her in bed. There was general clonus, tremor, excitation, grinding of teeth, and continuous picking of bedclothes. She was semiconscious, had an anxious expression, and became completely unmanageable.

Paraldehyde, 5 ml., phenobarbitone sodium, 3 gr. (0.2 g.), and promethazine hydrochloride, 50 mg. by injection, and pentobarbitone sodium and quinalbarbitone sodium, 3 gr. (0.2 g.) of each orally, were given with no effect. Finally chlorpromazine, 50 mg. by injection, two hours after the attack began, quieted her, and she fell asleep within half an hour. Iproniazid was now stopped, she having had a total of 4,400 mg. in 35 days. Next day she was calm and in a normal mental state; she had impaired memory of the events of the previous night. The next evening (June 1) she had a further bout of angina, suppressed with 200 mg. of pethidine by injection. Again a similar state of agitated hyperactivity developed, which was easily controlled with an injection of 50 mg. of chlorpromazine. Thereafter oral chlorpromazine was given, 50 mg. three times a day. A further attack of angina on June 3, for which 200 mg. of pethidine had to be injected, was not followed by restlessness. One week after iproniazid had been stopped postural hypotension and difficulty of micturition still persisted.

Liver-function Tests.—Serum bilirubin: direct, negative; indirect, 1 mg. per 100 ml.; thymol turbidity, 3 units; zinc flocculation, 9 units; colloidal gold, 0; alkaline phosphatase, 3.9 units; serum transaminase, 30 units per ml. Serum proteins: total, 5.8 g. per 100 ml. (albumin 4 g., globulin 1.8 g.). Electrophoresis of proteins showed no rise of γ-globulin. Urine analysis showed no abnormalities.

Discussion

In a recent symposium on the biochemical and clinical aspects of iproniazid Kline (1958) reported that jaundice was the most serious side-effect of the drug. One of us (S. B.) has studied two cases of iproniazid jaundice; his findings are reported at p. 1068. Hepatic dysfunction in the absence of jaundice has been reported by Scherbel (1958) in the treatment with this drug of patients suffering from rheumatoid arthritis. Four of his cases suddenly developed restlessness and hyperactivity. Laboratory investigations showed an increase in bromsulphthalein retention, a diminution of pseudo-cholinesterase, and a disturbance of proteins with an increase of γ-globulin.

Fouts and Brodie (1956) found that iproniazid inhibits the enzyme system in the liver responsible for detoxication of various drugs—for example, barbiturates, amphetamine, aminopyrine, and acetanilid. This study, together with that of Randall (1958), explains the potentiation of these drugs by iproniazid. He also suggests that the toxicity of iproniazid may result from this enzyme inhibition.

Pethidine is de-esterified and demethylated in the liver (Goodman and Gilman, 1955), and it is now recommended that this drug should not be used in patients suffering from severe liver disease, as exaggerated responses, especially cerebral excitation and confusion, may occur (Dundee and Tinckler, 1952).

There was a clear temporal relationship in our patient between the administration of pethidine and each attack of cerebral excitement. Since pethidine was given in therapeutic doses, such exaggerated response could be interpreted as evidence of interference by iproniazid with the detoxicating mechanism of the liver. Such liver-function tests as were carried out were normal. It is unfortunate, however, that no test of bromsulphthalein retention was performed in our patient, since this is one of the most sensitive tests available (Neefe *et al.*, 1955).

Randall has shown that iproniazid has a cumulative effect, and this may explain why our patient, who was receiving pethidine frequently, developed signs of central nervous system intoxication only during the fifth week of iproniazid treatment. The slow excretion of iproniazid accounts for the persistence of the ganglion-blocking effect as well as the exaggerated response to pethidine after its withdrawal.

Among the many reports dealing with the toxic effects of iproniazid upon the central nervous system, we found only one other instance where the first signs of toxicity appeared after pethidine (Mitchell, 1955). A patient with tuberculosis who had been taking 250 mg. of iproniazid a day for one month developed nausea and muscle-twitchings 20 minutes after 100 mg. of pethidine, which he used to take without side-effects. He became cyanosed, was sweating, and had a rapid pulse, exaggerated tendon reflexes, ankle clonus, and a bilateral plantar extensor reflex. This condition subsided

within 36 hours. He continued on the same dose of iproniazid for a further five months, during which time he showed signs of increasing restlessness, euphoria, insomnia, and other mild toxic effects. He died in coma after an acute illness characterized by fever, coarse tremor, hallucinations, and "auditory delusions." At necropsy the brain showed that death was due to haemorrhagic encephalitis; since no other cause was apparent this was believed to be due to the toxic effect of iproniazid.

The toxic manifestations of the central nervous system caused by pethidine and iproniazid are similar: cerebral excitation, confusion, restlessness, and muscle twitchings are common to both. It is difficult to decide whether in our own and Mitchell's case cerebral symptoms were caused by the simple additive effect of the two drugs or by a more complex inhibition of the enzyme-detoxicating system in the liver. The problem, however, is of theoretical interest. It is of practical importance that the two drugs become incompatible once a certain level of iproniazid is reached in the tissues. This may take up to four weeks.

The response to chlorpromazine was remarkable and perhaps a life-saving measure in our patient. Barbiturates commonly invoked in the treatment of cerebral excitation did not help, and in larger doses could have done actual harm if, as we have suggested, the liver detoxicating system was affected by iproniazid.

Although the pharmacological action on the heart is not yet clearly established, the improvement in this case and in others still under observation suggests that iproniazid is a promising drug in the treatment of angina. Patients with decubital angina, however, need heavy sedation with morphine analogues and barbiturates; potentiation with iproniazid may give rise to toxic cerebral reactions as in our patient. It is because of such therapeutic implications that this case is reported.

Summary

A case of decubital angina treated with iproniazid is reported. Although the frequency of the attacks diminished, occasional pethidine injections were still needed for the relief of pain. During the fifth week of iproniazid treatment these injections were followed by signs of severe cerebral irritation and excitement which responded dramatically to chlorpromazine. Either the simple additive effect of the two drugs or more complex interference with the normal detoxication of pethidine in the liver by iproniazid is believed to have caused toxic cerebral damage. It is suggested that pethidine should be used with caution in patients on iproniazid treatment.

ADDENDUM.—Since this paper was submitted a different complication of iproniazid treatment has been encountered in a 63-year-old man suffering from incapacitating angina of effort. On a dose of 50 mg. twice daily, much improvement resulted. One month later, while still on the same dose, he complained of difficulty of micturition and giddiness, and his blood pressure had fallen from 140/80 to 110/75. Iproniazid was discontinued, and then resumed after one week. A fortnight later he developed a small cerebral thrombosis, from which he fortunately recovered. Hypotension caused by iproniazid may have precipitated this complication.

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TREATMENT OF ULCERATIVE COLITIS WITH LOCAL HYDROCORTISONE HEMISUCCINATE SODIUM

A REPORT ON A CONTROLLED THERAPEUTIC TRIAL

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Two previous studies have dealt with the use of hydrocortisone applied topically to the colon in ulcerative colitis by means of a nightly rectal drip (Truelove, 1956, 1957). In the first study, 21 mild or moderate attacks of the disease were treated with hydrocortisone in the form of the free alcohol, and there were 14 rapid remissions, these remissions usually occurring in the first few days of treatment. However, although the sigmoidoscopic findings showed improvement in parallel with the clinical response, the histological picture as judged by biopsy specimens was little altered. As hydrocortisone itself is poorly soluble in water, the actual solution used for the rectal drip was prepared by diluting hydrocortisone dissolved in 50% ethyl alcohol with 10 times its volume of saline. There was the possibility that the weak alcoholic solution used as the vehicle for the hydrocortisone prevented the mucosa from healing.

In the second study, a compound freely soluble in water, hydrocortisone hemisuccinate sodium, was used. The clinical response was similar to that obtained with hydrocortisone itself in that there were 11 rapid remissions out of 18 courses of treatment. However, the histological picture of the colonic mucosa showed a favourable response in those subjects enjoying clinical remission, and it was therefore decided that the hemisuccinate (or some other water-soluble compound) was the corticoid of choice for this form of treatment.

The view that hydrocortisone applied topically is a useful form of treatment in this disease could be only presumptive on the results so far mentioned. In other words, this view rested solely on a personal clinical judgment that no considerable proportion of patients with an attack of ulcerative colitis would go swiftly into remission unless the treatment was having some strongly positive effect. Any student of ulcerative colitis must view with scepticism the use of a treatment based upon personal impressions, for the history of the disease includes a large variety of treatments which in their turn were introduced with enthusiasm on the strength of a few favourable responses and then slowly abandoned when they were found to be ineffective. The disease is one which manifests itself by exacerbations and remissions which are often unpredictable. Furthermore, a large body of opinion regards it as a psychosomatic disorder, so that a new form of treatment might possibly be beneficial for reasons unconnected with the pharmacological actions of the therapeutic agent. It is therefore essential that new forms of treatment should be put to formal tests so that patients are not exposed unnecessarily to useless methods of treatment.

Objects of the Present Study.—The main object of the present study was to compare the effect of hydro-