situation on the basis of the number of anginal attacks and the effort required to produce them. It should always be stopped before the patient returns to work.

Because of the danger of masking myocardial ischaemia, the numerous side-effects, and the risk of serious liver damage, iproniazid is not indicated for the patient with mild angina.

Although the drug could theoretically give rise to "silent infarction," this did not happen in any of our patients. Two of them had infarcts while receiving iproniazid. Both were at rest at the time and had typical pain.

The side-effects of iproniazid are described by Robitzek and Selikoff (1952) as, firstly, those referable to autonomic stimulation, including dryness of the mouth, constipation, delayed micturition, and difficulties in visual accommodation; secondly, those referable to central nervous system stimulation, including vertigo, muscle-twitching, hyperreflexia, excitement, euphoria, somnolence; and, thirdly, those referable to antagonism to vitamin B, including peripheral neuropathy. Unfortunately these and other side-effects limit the usefulness of the drug.

Summary

Iproniazid has been given to 40 patients with severe angina pectoris from occlusive coronary atherosclerosis, and was highly effective in reducing the frequency and severity of anginal attacks. It appears to act by blocking pain and not by improving the coronary circulation. Side-effects are common; many of our patients complained of giddiness and two developed pulmonary oedema, presumably from fluid retention. The blocking of angina may encourage the patient to be more active and may precipitate infarction. Because of this and the side-effects, the drug is not indicated for patients with mild angina pectoris. In the patient with severe and intractable angina it is of great value, especially if anticoagulant therapy can be given in addition. The patient can often be helped over a prolonged ischaemic episode, the drug being withdrawn when the condition improves.

We are grateful to Dr. Margaret Briggs, of Roche Products Limited, for her help and for supplies of marsilid.

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"We have learnt a great deal during the last three years from three reactor accidents which have led to partial melt-out of the reactor fuel elements. Although two of the reactors were put out of commission for a year and one was written off, no one was hurt by these accidents or received an overdose of radiation. The results of the accidents agree in a remarkable way with laboratory experimental work in showing that only a very small fraction of some of the bone-seeking isotopes escaped from the melted fuel. The disturbances due to these accidents were accordingly less than envisaged previously. Later generations of reactors than these early models are much better protected by containment and instrumentation, and some papers have shown considerable progress in advanced designs of containment which are thought to be proof against the maximum credible accident. This gives us considerable confidence in safe operations in the future, and we may, in due course, expect the location of plants in more populated areas. There has also been a growth of national reactor safety and inspection organizations, analogous to those in being for the aircraft industry. They inspect designs and prescribe codes of operation to help to maintain safety."—From a lecture by Sir JOHN COCKCROFT, F.R.S., to the Danish Society of Civil Engineers on October 6.

JAUNDICE ASSOCIATED WITH ADMINISTRATION OF IPRONIAZID

REPORT OF TWO CASES

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Iproniazid ("marsilid"; or 1-*iso*nicotinyl-2-*iso*propylhydrazine phosphate) is a variant of isoniazid, which was first used for its antituberculous properties in 1952. Then described as a drug which made patients "dance and sing in the ward" and as a "fountain of energy," it was discarded by chest physicians as too apt to produce side-effects, including psychotic episodes; it has since been hailed by psychiatrists as a powerful "energizer," and been found useful in the treatment not only of depressive states but also in angina pectoris and collagen diseases, gastro-intestinal conditions, etc. Zeller *et al.* (1952) found that iproniazid was a powerful inhibitor of amine oxidase. Udenfriend *et al.* (1957) were able to demonstrate a rapid and large rise in brain serotonin in animals given the drug. The effect of the drug on mood in humans has been attributed to this increase in serotonin.

In a symposium (1958) in New York in 1957 many preliminary studies were presented, but concluding speakers stressed the need for carefully controlled trials before definite claims for the value of the drug in psychiatric and other conditions could be made. During the course of such a trial in this hospital, two cases of jaundice have occurred. The possibility of this drug being hepatotoxic has recently been raised. In view of the increasing use of iproniazid in psychiatric practice, these cases seem worthy of immediate report.

Case 1

The patient, a 53-year-old working-class widow, had been subject to spells of agitation and depression, with increasing suspiciousness and misinterpretation for three years. She was previously hardworking and loyal, and had struggled to bring up five children, one of whom was diabetic from infancy. She had had no serious illness previously, and had never been jaundiced. She had not received injections and there was no contact with cases of infective hepatitis.

She was admitted to hospital on October 11, 1957, and made a good initial response to hospitalization. Iproniazid was first given at 150 mg. daily on January 11, 1958, and reduced to 100 mg. daily on February 11. During the first week of March she began to feel vaguely unwell, suffered from giddiness and palpitations, and later complained of superficial pains in the limbs and shivering attacks. All but the latter symptoms have been described as side-effects and are often encountered in iproniazid therapy. Our patient minimized these for fear that she might be taken off the drug, which was helping her considerably. On March 24, however, she developed mild anorexia with constipation and took to her bed. Iproniazid was discontinued. Two days later, though subjectively much improved, she was jaundiced and had a pale stool and biliuria.

On examination the liver edge, slightly tender, could be palpated two fingerbreadths below the costal margin, but liver dullness was not greatly increased. She was, and remained, apyrexial. (For details of investigations, see Table.) With a low-fat diet, rest, and vitamins her strength and

appetite improved further, though jaundice deepened. On April 6, however, there was a return of anorexia and nausea was persistent. Her clinical condition deteriorated, some petechiae appeared, hepatomegaly was no longer demonstrable, but the spleen was found to be enlarged and easily palpable. Rubefacience, circumoral pallor, with "cherry-red" lips and red palms, were observed. There was no tremor or other signs of encephalopathy. Subacute hepatic necrosis was diagnosed, and our findings were confirmed by Dr. Philip Harvey, who kindly saw the patient and on April 9 arranged her transfer to St. Stephen's Hospital for further investigation and treatment.

Intravenous corticotrophin in dextrose was immediately given, the patient receiving a total of 600 units over a period of three days. Diet was restricted to 1,500 calories (with 35 g. of protein). Neomycin and tetracycline were given orally, together with soluble insulin (5 units before meals) and propyltestosterone, these measures aiming at diminishing protein katabolism. Vitamin K, folic acid, and vitamin B_{12} completed the regime. Twelve hours after initiation of this therapy icterus had greatly diminished. The serum bilirubin level had fallen from 16.6 to 6.4 mg. at the end of corticotrophin administration; by April 25 this level had fallen to 2.8 mg., and her recovery has since been uninterrupted.

A liver biopsy, performed by Dr. Gordon Signy on April 14 (after completion of the corticotrophin treatment), was reported as follows: "There are widespread fatty changes. There are focal areas of swollen hepatic cells and some bile thrombi, focal areas of infiltration, with small cells, including lymphocytes, polymorphs, and eosinophils, mostly occurring round the central vein. There is some increase of collagen fibres around the central vein and the portal spaces. The picture is one of focal necrosis." An electrocardiogram showed sinus bradycardia only. The white blood count remained within normal limits, and the sedimentation rate was not raised.

Case 2

A 31-year-old single woman, secretary to a business executive, had been admitted for the third time to Bethlem Royal Hospital in September, 1957, on account of severe and disabling neurotic symptoms accompanied by depressive features. After discharge from hospital in January. 1958, she remained apathetic, mildly depressed, and unable to work.

Iproniazid was given on January 31 in doses of 150 mg. daily and continued until April 12. Soon after initiation of this therapy she was able to resume work, and remained so well that she failed to keep her out-patient appointments. At the beginning of May she began to feel ill, nauseated, tense, and depressed, but attributed such symptoms to her anxiety relating to a difficult emotional situation. Nausea had been a frequent feature of her various neurotic illnesses.

When seen in the out-patient department on May 9 she appeared agitated and depressed. Iproniazid was again prescribed in doses of 75 mg. daily, combined with chlorpromazine, 150 mg. daily. Later that day she noticed that her urine was dark and her stools were pale. On the following day jaundice appeared. Iproniazid and chlorpromazine were discontinued after only a few doses. When she reported sick to her firm's medical officer she was found to be pyrexial, and on examination the liver was palpable and tender. "Toxic jaundice" was diagnosed, and she was sent home to bed and treated with a fat-free diet. She had not received injections and there was no contact with other cases of jaundice. Unfortunately, we were not informed of these events until May 30, by which time the jaundice was resolving. She was visited at her home on June 1. On examination she was still slightly jaundiced, the liver edge was palpable but not tender, there was no splenomegaly, and haemorrhage and other skin manifestations were absent. After this visit she was admitted to St. Stephen's Hospital, and a liver biopsy was carried out by Dr. Gordon Signy on June 6. The tissue obtained proved to be part of a haemangioma, and no information could be obtained from the few liver cells present in the sections. The patient suffered no after-effects and was discharged home.

Laboratory Investigations on June 1.—Serum bilirubin: direct, positive; indirect, 2.3 mg.; thymol turbidity, 3 units; zinc flocculation, 9 units; colloidal gold, 0; alkaline phosphatases, 9.6 units; serum transaminase, 47 units; Total protein, 6.5 g. (albumin 4.2 g., globulin 2.3 g.). Electrophoresis showed that the α_2 pattern was less prominent than usual. Abnormality of gamma-globulin was not found.

Discussion

Jaundice was reported during iproniazid administration in tuberculous patients (Bosworth *et al.*, 1955; Ogilvie, 1955). Although only one more case has been published since then (deVerteuil and Lehmann, 1958), jaundice was referred to by Kline (1958) as the most serious complication of iproniazid treatment. The incidence of this jaundice is estimated to be under 0.05% and to approximate that of infective hepatitis (Marks, personal communication). The mortality rate, however, is higher than that reported in infective hepatitis.

The five cases reported during treatment of tuberculosis recovered, but the case reported by deVerteuil and Lehmann, occurring during a trial of iproniazid on 31 depressed and apathetic patients, was fatal. Necropsy in this case showed a "hepatic necrosis of the type sometimes seen in response to toxic agents."

Scherbel (1957a) has described four cases of jaundice in a trial of isoniazid and iproniazid in rheumatic arthritis. In two of his patients there was evidence of previous liver damage: one patient was alcoholic and had a portal cirrhosis and the other, previously subjected to cholecystectomy, had a biliary cirrhosis. The liver biopsies presented a picture typical of "viral hepatitis." The serum bilirubin was 7.2 mg. in the most severe of his cases. Unfortunately, it is not clear from his report whether the patients were receiving isoniazid or iproniazid when jaundice occurred.

During the course of the above clinical trial Scherbel (1957b) described a state of behavioural hyperactivity in some of his patients who were receiving iproniazid. Labora-

Table of Laboratory Investigations

	March 26	April 2	April 11	April 14	April 25	May 6	May 24
Bilirubin	4·2 mg.	19·4 mg.	16·6 mg.	6·4 mg.	2·8 mg.	1·4 mg.	0·6 mg.
Alkaline phosphatases	18·8 u.	19 u.	26·7 u.	—	—	7 u.	—
Thymol turbidity	6 u.	3 ,,	2 u.	—	—	3 ,,	—
Thymol flocculation	Neg.	Neg.	Neg.	—	—	Neg.	—
Zinc turbidity	7 u.	6 u.	6 u.	—	—	3 u.	—
Colloidal gold	—	—	—	Neg.	—	—	—
Total protein	6·1 g.	7·1 g.	—	—	—	7·4 g.	8·6 g.
Albumin	3·8 ,,	3·6 ,,	—	—	—	3·9 ,,	5·9 ,,
Globulin	2·3 ,,	3·5 ,,	—	—	—	3·5 ,,	2·7 ,,
Serum transaminase	—	—	160 u./ml.	—	—	—	—
Prothrombin time	—	—	—	19 sec. (14 sec. control)	—	—	—
Blood urea	—	—	—	29 mg.	—	—	—
Haemoglobin	10·9 g.	—	—	12·7 g.	—	12·7 g.	—
Urine	Urobilin+ Urobilinogen— not detected	—	Bile—trace Urobilin—excess Urobilinogen—excess	—	Urobilin—trace Urobilinogen— not detected		

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.

We thank Dr. R. F. Hobson and Dr. J. G. Hamilton, under whose care the patients were admitted, for permission to publish this report, and Dr. Linford Rees for his advice and encouragement. To Dr. Philip Harvey we are indebted for seeing and treating our patients; and to Dr. Gordon Signy for performing the liver biopsies. Dr. J. Marks, of Roche Products Ltd., supplied the marsilid for our clinical investigation and provided us with much unpublished information.

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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