their response to the drug is made on the following basis: "Much improved" is limited to relief sufficiently pronounced to allow discharge of the patient on a maintenance dose of the drug. "Somewhat improved" indicates obvious benefit of some symptoms with continuation of others. "No relief" included temporary or slight relief.

It will be seen that only 6 out of 67 patients showed any improvement on reserpine, while none of 17 patients showed improvement on rauwolfia.

In group A, three patients felt equally improved on active drug and placebo, and were obviously discounted. Four patients felt improved while taking the placebo. One patient felt worse during a month on placebo; another felt worse on active drug and placebo. None of the patients in this group felt improved while taking only active drug.

In group B, one patient was "much improved" and five were "somewhat improved." Four of these patients were diagnosed as having anxiety states, of whom two were suffering from tension, one from somatic dysfunction (skin disorder), and one from phobias; one patient suffered from an obsessive compulsive neurosis; and the sixth suffered from reactive depression. Three of these patients suffered from hypertension. Thirteen patients treated with reserpine showed temporary improvement only ("no relief").

Complications.—Foote (1955) observed three cases of oedema of the legs, including one with oedema of the face, in 32 psychotics receiving 4 mg. of reserpine daily. Richman and Tyhurst (1955) report the appearance of extrapyramidal signs and symptoms in 12 out of 19 patients receiving 3–13 mg. of reserpine intravenously and 0.5–5 mg. orally. The occurrence of depression reported by Freis has already been mentioned. In our series seven patients complained of nasal stuffiness, four of unpleasant or excessive dreaming, two of conjunctival irritation, three of looseness of the bowels at the beginning of treatment, and four of slight drowsiness. Four patients observed a gain in weight. The complications recorded with larger doses were not seen in our series.

Discussion

In view of the enthusiastic reports quoted, the result of this work was disappointing, using as we did the dosage suggested by Kline for neuroses. Much larger doses have been used with psychotic patients. A number of useful points do arise, however, as a guide to the possible value of these drugs in selected cases. Eight hypertensive patients in the 75 treated provided three out of the six improved cases; they showed a reduction of tension and irritability, and a reduction of blood pressure in two. Apart from a reduction of anxiety in the other three improved cases no other common factor was established. It was observed that side-effects were more often encountered among the improved than the unimproved cases, indicating a possible sensitivity to the drug.

In group A, of the 21 patients treated with reserpine, none improved; but in group B, of 40 treated with reserpine six improved. These results suggest a possible discrepancy in the methods of assessment.

The patients who felt equally improved on both the active drug and the placebo, or on the placebo alone, had experienced either a change in circumstances or were unduly suggestible, as were so obviously the one or two patients who complained of side-effects whilst receiving the placebo. This supports the contention that controlled experiments are desirable in any investigation involving the use of new drugs if their value is to be accurately assessed.

A number of inadequate personalities were treated, mainly in the chronically anxious, depressive, hypochondriacal, and self-conscious groups. Not one of these patients showed any real benefit. Tonge (1955) found equally unrewarding the treatment of a group termed "neurasthenic psychopaths." The inclusion of these patients in this study may account to some extent for our disappointing results.

Where a neurosis occurs in the setting of a good basic personality, individual psychotherapy must remain the treat-

ment of choice. A few patients spontaneously expressed the opinion that amylobarbitone had helped them more effectively in the past. In the presence of tension, chlorpromazine may be found useful (Garmany *et al.*, 1954).

The suggestion of Kline that rauwolfia reduces obsessive-compulsive drives and overcomes excessive inhibition and reticence has not been confirmed. Anxiety in association with hypertension, however, is apparently reduced with reserpine.

Summary

An investigation of the effects of rauwolfia and reserpine upon 75 psychoneurotics failed to confirm the results claimed in a number of psychiatric disorders. The need for adequate control in such investigations is stressed.

Six patients benefited, of whom three were hypertensive. Side-effects were infrequent and slight in nature.

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REFERENCES

- Foote, E. S. (1955). *British Medical Journal*, 1, 1192.
 Freis, E. D. (1954). *New Engl. J. Med.*, 251, 1006.
 Garmany, G., May, A. R., and Folkson, A. (1954). *British Medical Journal*, 2, 439.
 Hakim, R. A. (1953). Quoted by Kline (1954).
 Kline, N. S. (1954). *Ann. N.Y. Acad. Sci.*, 59, 107.
 Noce, R. H., Williams, D. B., and Rapaport, W. (1954). *J. Amer. med. Ass.*, 156, 821.
 Richman, A., and Tyhurst, J. S. (1955). *Canad. med. Ass. J.*, 72, 457.
 Schlittler, E., MacPhillamy, H. B., Dorfman, L., Furlenmeier, A., Huebner, C. F., Lucas, R., Mueller, J. M., Schwyzler, R., and St. André, A. F. (1954). *Ann. N.Y. Acad. Sci.*, 59, 1.
 Tonge, W. L. (1955). *British Medical Journal*, 1, 1066.
 Vakil, R. J. (1949). *Brit. Heart J.*, 11, 350.
 Wilkins, R. W., and Judson, W. E. (1953). *New Engl. J. Med.*, 248, 48.
 Winsor, T. (1954). *Ann. N.Y. Acad. Sci.*, 59, 61.

JAUNDICE IN RELATION TO CHLORPROMAZINE THERAPY

BY

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The occurrence of jaundice in relation to chlorpromazine therapy is becoming well known. We report four further cases of this complication encountered during a relatively small experience with the drug. We have also obtained information by questionnaire of the occurrence of this complication in the experience of other physicians, and present certain facts and inferences.

We have given chlorpromazine to 26 patients (8 males, 18 females) for the prevention and treatment of nausea and vomiting. Their ages ranged from 8 to 65 (mean 45). The conditions treated included radiation sickness, pregnancy sickness, uraemia, cerebral tumour, "cyclical" vomiting, and therapy with morphine, diamorphine, pethidine, mustine hydrochloride, oestrogens, and digitalis. The usual dose of chlorpromazine was 25 mg. thrice daily and the duration of treatment one week. The largest daily dose was 100 mg. and the greatest duration of treatment 14 days. Jaundice developed in three of these patients.

Case Reports

Case 1.—A woman of 60 with carcinoma of the breast and metastases developed troublesome nausea and vomiting during large-dose oestrogen therapy. She was given chlorpromazine, 25 mg., by mouth twice daily for five days, then 25 mg. once daily for a further seven days. On the sixth day of chlorpromazine therapy mild jaundice was noted, with bile in the urine and pale stools, but there was no general upset. Chlorpromazine therapy was continued. The jaundice subsided at the end of one week. Liver-function tests showed a rise in the serum bilirubin and alkaline phosphatase with normal thymol turbidity. The patient died eight months later from multiple metastases, but suffered no recurrence of jaundice.

Case 2.—A woman of 39 with carcinoma of the breast was vomiting persistently during large-dose oestrogen therapy, and was therefore given chlorpromazine, 25 mg., twice daily for two days. This drug was then stopped because of drowsiness. Two days later jaundice appeared, and this had the clinical and biochemical features of obstructive jaundice. Jaundice persisted until the patient's death in coma two weeks later. At necropsy a large metastatic tumour mass was found in the temporal lobe, and this was thought to have been responsible for the patient's deepening coma. The liver showed regular central lobular necrosis with mid-zone fatty infiltration. The small bile ducts were compressed, and some contained bile thrombi, but the larger ducts were patent. Cellular infiltration of the portal tract was inconspicuous. This patient had had a transient attack of jaundice, thought by her general practitioner to be due to infective hepatitis, ten weeks before her death.

Case 3.—A woman of 62 died of acute necrosis of the liver two weeks after an operation for the relief of calculus obstruction of the common bile duct. Bowel haemorrhage and paralytic ileus had preceded death. The patient had received 25 mg. of chlorpromazine four times daily for two days early in the post-operative period in an unsuccessful attempt to relieve post-operative vomiting. In this case chlorpromazine may have played a part in the pathogenesis of acute liver necrosis.

Case 4.—A woman aged 30 was referred from the psychiatric unit. She had received chlorpromazine, 75 mg., thrice daily for seven days for treatment of an anxiety state. Thirteen days after stopping treatment she developed jaundice of obstructive type with pyrexia, abdominal pain, vomiting, enlargement of the liver, pruritus, bilirubinuria, and pale stools. The jaundice deepened, then gradually cleared after 14 days. Subsequent cholecystograms and liver-function tests were normal.

Results of Questionnaires

Because of the varying relationship between chlorpromazine therapy and jaundice in these four patients we sought additional information on their relationship through the medium of a questionnaire addressed to five psychiatric units in Scotland where chlorpromazine was known to be in use. Further, through the courtesy of Dr. John Harper, of Messrs. May and Baker, there were made available to us for analysis the results of a large questionnaire addressed by Messrs. May and Baker in the autumn of 1954 to 57 centres in the United Kingdom and Eire, mainly psychiatric units, where chlorpromazine was being extensively used. Data are thus available concerning 3,252 patients treated with chlorpromazine, of whom 39 developed jaundice, an apparent incidence of 1.2%. Because of varying periods of observation, different types of patient treated, and different dose schemes used, this figure offers only an approximation of the extent of the problem. The data provided by the questionnaire were not always complete in all respects, but it was possible to draw the following inferences.

Age.—Jaundice was rather more common in older than in younger patients. The youngest patient to develop jaundice was aged 23, and the oldest 81.

Sex.—Jaundice was commoner in females than in males in the proportion of 2 or 3 to 1.

Route of Administration.—Jaundice occurred in patients treated by oral therapy alone, by oral plus intramuscular therapy, and by intramuscular therapy alone.

Dose and Duration of Therapy.—The daily dose of chlorpromazine in patients who developed jaundice ranged from 50 to 800 mg., but in over three-quarters of the cases it was under 200 mg. The duration of therapy ranged from 2 to 35 days, most cases occurring in the second, third, and fourth weeks of treatment. The total dose of chlorpromazine that had been given at the time that jaundice appeared ranged from 100 mg. to 10 g., and was in most cases between 1 and 6 g. In nine cases (including Cases 3 and 4, above) jaundice did not appear until after chlorpromazine was stopped. The duration of therapy in these cases was from 2 to 28 days (mean, 16 days), and the jaundice appeared 5 to 14 days after stopping treatment. It is not possible to be sure that the jaundice in these cases was causally related to chlorpromazine, but the high incidence is suggestive; and, except in our own cases, no other cause of jaundice was usually evident.

Course.—In one further case jaundice was fatal. A female mental hospital patient aged 81 received 1,750 mg. of chlorpromazine over 24 days. Five days after the conclusion of treatment she developed jaundice, with enlargement of liver and pale stools. Jaundice persisted until the patient's death two and a half months later. In another case the patient recovered from jaundice despite continued administration of chlorpromazine (cf. also Case 1, above). The patient received 150 mg. of chlorpromazine daily and became jaundiced on the seventeenth day of treatment. The drug was continued and jaundice subsided within a fortnight. As a rule jaundice cleared within two weeks of stopping the drug, but in a few cases it persisted for a month or more, as in the case just described.

Predisposing Factors.—Pre-existing liver disease, which is now taken to be a contraindication to chlorpromazine therapy, was present in our Cases 2 and 3, and also in a mental hospital patient who developed coma and died four days after starting treatment. There was no jaundice, and the cause of coma was not evident. Post-mortem examination revealed multilobular cirrhosis of the liver, which must have been present before chlorpromazine was given. On the other hand, several of our patients who received chlorpromazine without developing jaundice had pre-existing liver disease; and, in fact, one patient with jaundice associated with accidental haemorrhage received three doses of 25 mg. of chlorpromazine without apparent harm. Concomitant administration of other drugs might predispose to liver damage from chlorpromazine, and, in fact, our Cases 1 and 2 received large doses of oestrogens. One other patient who developed jaundice during chlorpromazine therapy had been given large amounts of mepacrine for the treatment of rheumatoid arthritis. There is no evidence that any of the patients suffered from dietary deficiency.

Clinical Features.—We have attempted to classify the cases into four clinical types. (1) Mild transient jaundice with pale stools and bile in the urine but little systemic upset. Jaundice cleared in a few days even if chlorpromazine was continued. (2) Pyrexia of about 101° F. (38.3° C.), epigastric pain and tenderness, anorexia, nausea, and vomiting ushered in an attack of jaundice of moderate severity lasting two to four weeks. Enlargement of liver, pale stools, dark urine. Elevation of serum bilirubin and alkaline phosphatase. Tests of hepatocellular function, normal. (3) Severe prolonged jaundice, sometimes with death from liver failure. (4) In some cases, not hitherto discussed here, pyrexia, anorexia, and epigastric pain and tenderness occurred, with elevation of the E.S.R. but without frank jaundice.

Discussion

On the whole the features of jaundice in patients treated with chlorpromazine described here are supported by reports in the recent literature (Boardman, 1954; Earle,

1955; Grytting, 1954; Hartnett, 1955; Loftus *et al.*, 1955; Lomas *et al.*, 1955; Van Ommen and Brown, 1955; Whitfield, 1955; Zatuchni and Miller, 1954). The main points on which comment seems justified at present are:

1. The jaundice is apparently *not* a direct toxic action of chlorpromazine on the liver. This is supported by (a) the demonstrated lack of correlation between the amount of chlorpromazine ingested and the occurrence of jaundice; (b) the absence of liver damage in patients who have taken large amounts of chlorpromazine in suicidal attempts (Deniker, 1954; Aubertin *et al.*, 1954; Vallat and Lepetit, 1954); (c) the failure to induce liver damage in experimental animals given large doses of chlorpromazine over long periods (Courvoisier *et al.*, 1953; Smith, Kline, and French, 1954, personal communication); (d) the failure to demonstrate reduction in the oxygen consumption of isolated rat-liver slices exposed to chlorpromazine (Peruzzo and Forni, 1953); (e) the observation that in some patients jaundice is not apparent until some time after the drug has been stopped.

2. Older people are more likely to develop jaundice than young ones, and females more than males.

3. The mechanism of jaundice in our Case 2 and in other recorded cases is intrahepatic biliary obstruction (Sherlock, 1955). In some cases the bile ducts are apparently compressed by swollen fat-filled liver cells, and the cause of fat storage in these cases might be worth investigating. It seems necessary to explain why, on the one hand, jaundice does not appear until after chlorpromazine therapy has been stopped, and, on the other hand, why the jaundice can recover even although chlorpromazine is continued. The sex incidence of this complication also awaits explanation.

Conclusion

The incidence of jaundice in patients receiving chlorpromazine therapy is about 1%, and many cases are mild. However, in circumstances not clearly delineated severe or fatal liver disease can occur. It would seem wise to avoid chlorpromazine therapy in the following circumstances: (1) when infective hepatitis is endemic; (2) in the presence of liver disease; (3) in malnourished patients; (4) when other potentially hepatotoxic agents have been used; and (5) when oestrogens have been given. Should a pyrexial illness occur during chlorpromazine therapy evidence of liver damage should be sought. If it is found, chlorpromazine and all other drugs should be withdrawn and a high-protein high-calorie diet given.

This advice is largely empirical, and more clinical and experimental information is required before the problem of jaundice and chlorpromazine is elucidated.

Summary

During the treatment of 26 patients with small doses of chlorpromazine for relief of vomiting, three cases of jaundice occurred; a fourth case was referred from a psychiatric unit. The clinical features of these cases are analysed together with 39 additional cases, information about which was obtained by questionnaire. The incidence of jaundice in chlorpromazine therapy was about 1%. Jaundice was more common in females than in males, but bore no relation to the dose and duration of therapy. Cases varied in severity from mild and transient jaundice to severe, prolonged, and occasionally fatal illness. It is advised that chlorpromazine be avoided in the presence of epidemic hepatitis, in patients with liver disease, and in combination with other potentially hepatotoxic agents.

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REFERENCES

- Aubertin, A., Martin-Dupont, C., and Tavernier, J. (1954). *Presse méd.*, 62, 752.
 Boardman, R. H. (1954). *British Medical Journal*, 2, 579.
 Courvoisier, S., Fournel, J., Ducrot, R., Kolsky, M., and Koltschet, P. (1953). *Arch. int. Pharmacodyn.*, 92, 305.
 Deniker, P. (1954). Quoted by H. Azima, and W. Ogle, *Canad. med. Ass. J.*, 1954, 71, 116.
 Earle, B. V. (1955). *British Medical Journal*, 1, 1156.
 Grytting, G. (1954). *Nord. med.*, 52, 1699.
 Hartnett, B. S. (1955). *British Medical Journal*, 1, 1458.
 Loftus, L. R., Huizenga, K. A., Stauffer, M. H., Rome, H. P., and Cain, J. C. (1955). *J. Amer. med. Ass.*, 157, 1286.
 Lomas, J., Boardman, R. H., and Markowe, M. (1955). *Lancet*, 1, 1144.
 Peruzzo, L., and Forni, R. B. (1953). *Presse méd.*, 61, 1463.
 Sherlock, S. (1955). *Diseases of the Liver and Biliary System*. Oxford.
 Vallat, J.-N., and Lepetit (1954). *Presse méd.*, 62, 752.
 Van Ommen, R. A., and Brown, C. H. (1955). *J. Amer. med. Ass.*, 157, 321.
 Whitfield, A. G. W. (1955). *British Medical Journal*, 1, 784.
 Zatuchni, J., and Miller, G. (1954). *New Engl. J. Med.*, 251, 1003.

HYSTERICAL ABDOMINAL PROPTOSIS

RECORDS OF A CASE

BY

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Our attention was recently drawn, for the first time, to a most interesting paper by Roussak (1951) on a clinical condition which he called "hysterical abdominal proptosis." On reading it we were reminded vividly of a patient who was under our care two years ago and who presented an interesting problem in diagnosis and in management.

Case Report

A short, thick-set, rugged, placid trawlerman aged 55 first came under the care of one of us (J. H. D. M.) on account of shortness of breath and of abdominal distension. Although he was acutely dyspnoeic there was no cyanosis. His heart was apparently normal, as was an x-ray film of his chest, although on clinical examination there was poor aeration at the bases. The most striking feature on physical examination, however, was the prominence of the abdomen, which was grossly distended and tympanitic all over. Despite a diligent search, no cause for this distension was discovered, and at a subsequent laparotomy there was no hint of intestinal obstruction. However, as soon as anaesthesia was induced the abdominal swelling collapsed in a most dramatic fashion, only to reappear with the return of consciousness. A second anaesthetic was administered during his convalescence and with precisely the same result (Fig. 1).

He was later admitted to Hammersmith Hospital, where it was thought possible that his dyspnoea might be due to a slight degree of left ventricular failure. While a variety of investigations were being completed he continued to complain of abdominal distension, which remained unchanged for days on end. There was no disturbance of bowel function or any colic or vomiting. A straight x-ray film of the abdomen showed only the normal amount and distribution of intestinal gas, and the diaphragm was at its proper level and moved reasonably well. However, as soon as