Adult Fanconi Syndrome and Cirrhosis

SIR,—In 1947 we published a paper¹ entitled "Studies on the Mechanism of the Fanconi Syndrome." The subject of the study was a man aged 34, presenting in 1945 with gross osteomalacia. He was found to have the full renal-tubular abnormalities usually associated with the name "Fanconi syndrome"—namely, renal tubular reabsorptive defects of phosphate, glucose, and amino-acid, with renal-tubular acidosis. He was also found to have severe cirrhosis, from which he died in early 1946, his bone disease having been largely controlled by treatment. We thought then that cirrhosis was an occasional association of "Fanconi syndrome," indeed we then speculated that the cirrhosis might have resulted from amino-acid depletion in consequence of the amino-aciduria.² (We do not believe this any longer.)

Our subsequent clinical studies at University College Hospital have shown that cirrhosis is only consistently associated with a childhood form of the Fanconi syndrome, as in the case described by Baber.³ One of us (C. E. D.) began to get worried about the original case in an adult man, since no further similar "idiopathic" cases have since been seen or heard of in this age group. The post-mortem material was no longer available, but a measured aliquot of the patient's 24-hour urine of 7 January 1946 has been traced in our cold room. It has been sent to Professor J. N. Cumings, who reports that it contained 45 µg./100 ml. of copper, or 594 µg. in the 24-hour specimen. He adds that this grossly excessive excretion is "undoubtedly diagnostic of Wilson's disease if it cannot be explained by contamination."

It would seem necessary to record now that the diagnosis of "idiopathic adult Fanconi syndrome with cirrhosis of the liver" probably no longer exists on the basis of present evidence. Any apparent case should therefore be carefully screened for causes of secondary renal tubular or of liver dysfunction such as myeloma, and heavy-metal poisoning—but especially for Wilson's disease, for which we now have excellent treatment.⁴

The existence of adult Fanconi syndrome without cirrhosis remains fully substantiated.—We are, etc.,

C. E. DENT.

University College Hospital
Medical School,
London W.C.1.

J. M. STOWERS.

Royal Infirmary,
Aberdeen.

REFERENCES

- 1 Stowers, J. M., and Dent, C. E., *Quart. J. Med.*, 1947, 16, 275.
- 2 Himsworth, H. P., *The Liver and its Diseases*, 1947, p. 98. Blackwell, Oxford.
- 3 Baber, M. D., *Arch. Dis. Child.*, 1956, 31, 335.
- 4 Morgan, H. G., Stewart, W. K., Lowe, K. G., Stowers, J. M., and Johnstone, J. H., *Quart. J. Med.*, 1962, 31, 361.

Anaesthesia and Monoamine-oxidase Inhibitors

SIR,—The monoamine-oxidase inhibitors are widely used in the psychiatric treatment of depression. There is, therefore, an increasing number of patients who may require an operation whilst they are taking these drugs. It is known that very occasionally such patients show a profound reaction if they are given either an analgesic or a vasopressor drug.¹⁻⁴

Recent reports on the anaesthetic management of patients on monoamine-oxidase inhibitors have suggested two possible courses.^{5,6} First, that the therapy is discontinued and the surgery is postponed for at least two weeks; or secondly, that a local-analgesic technique without the addition of vasopressor drugs is used. Neither of these suggestions is ideal—to discontinue the monoamine-oxidase drug may lead to a recurrence of the depression: and to produce satisfactory local analgesia for certain operations may well be beyond the capabilities of many anaesthetists—besides the whole procedure being an ordeal for a patient deprived of the customary preoperative sedation. Furthermore, although general anaesthesia with modern techniques can be performed without preliminary sedation, powerful analgesic drugs are needed after all but the most trivial operations.

Since only a very small percentage of patients who are taking these drugs show a sensitivity reaction it would seem a more rational approach to this problem to try to test beforehand for any such sensitivity to either analgesic or vasopressor drug. The system is simple and has been satisfactorily used in eight patients receiving full doses of monoamine-oxidase inhibitors. The sensitivity test for analgesics is carried out in the following manner:

The patient's blood-pressure, pulse, and respiration are first measured and charted. The general state of awareness is also noted. Then either 5 mg. pethidine or 0.5 mg. morphine are injected intramuscularly. The vital signs, together with any change in the level of consciousness, are then observed and recorded at five-minute intervals for the next 20 minutes, after which they are noted and charted every 10 minutes for the remainder of the first hour. At the end of this period, if there has been no obvious change, then either 10 mg. of pethidine or 1 mg. of morphine is given and the whole process repeated for the second hour. Again, at the end of the second hour, if there has been no obvious change, a further dose of 20 mg. of pethidine or 2 mg. of morphine is given. After three hours, if no change has developed, then 40 mg. of pethidine or 4 mg. of morphine is given. It is unnecessary to carry the test beyond this stage, since any sensitivity response would have been apparent by the time this stage had been reached.

In one patient the injection of 5 mg. of pethidine produced a fall in systolic blood-pressure of 30 mm. Hg, a rise in the pulse rate of 20 beats per minute, and some slight drowsiness; whereas in the remaining seven patients there was no obvious change in the vital signs.

The advantage of using such a sensitivity test is that it can be carried out even if only a few hours are available before operation, and the injection at the third hour, with what remains from the previous injections, can be used as the premedication. Once it is known that the patient does not respond in an abnormal manner to these drugs then they can be used freely in the treatment of pain in the post-operative period. On this basis there is the minimum of disruption of the normal therapeutic procedure.—I am, etc.,

H. C. CHURCHILL-DAVIDSON.

Department of Anaesthetics,
St. Thomas's Hospital,
London S.E.1.

REFERENCES

- 1 Palmer, H., *Brit. med. J.*, 1960, 2, 944.
- 2 Shee, J. C., *ibid.*, 1960, 2, 507.
- 3 Reid, N. C. R. W., and Jones, D., *ibid.*, 1962, 1, 408.
- 4 Taylor, D. C., *Lancet*, 1962, 2, 401.
- 5 Perks, E. R., *Anaesthesia*, 1964, 19, 376.
- 6 Deacock, A. R. de C., and Harnik, E., *ibid.*, 1964, 19, 454.

Skin Conditions in Children

SIR,—I would like to thank Dr. Martin Beare for his excellent account of skin conditions in infancy and childhood (16 January, p. 171, and 23 January, p. 233) as it contains a great deal of helpful common sense.

I also congratulate him on being able to distinguish so clearly between the seborrhoeic pattern of eczema in infancy and childhood and that of "true" infantile eczema or atopic eczema. Many of us find this is very difficult, as mixtures of the two patterns seem to be so common and a child may have predominantly one pattern, only at a later stage to have a distribution more in keeping with the other. A family history of eczema, asthma, and hay-fever—or the development of these conditions—is commoner with the atopic pattern, but they are by no means uncommonly associated with distributions of eczema of the seborrhoeic pattern. Recently I have tried applying similar criteria to those mentioned by Dr. Beare in his differential diagnostic table, and whereas it is possible to say some patients have predominantly the seborrhoeic eczema pattern and some the atopic pattern the majority seem to have mixtures of the two.

I am worried about the bad prognosis which is given under the heading of atopic eczema, as the casual reader might get the impression that their patients, and indeed often their own children, are "doomed to a life of either eczema or asthma." Eczema, to a degree requiring medical attention at some time, occurs in about 1 in 30 normal children.¹ In minor grades it is even commoner than this. It is true that we see many patients who do continue to have eczema throughout childhood and in adult life, and in the very severe grades who have required admission to hospital some 50% develop asthma.² This type of case often has to be seen frequently by dermatologists and general practitioners, and this may give a wrong impression of the incidence of serious trouble compared with the vast number of children who have eczema at some time. Dr. Beare does indeed apply his bad prognosis to "the moderately severe or severe atopic." I personally would give a much happier prognosis and would say that the majority of children with this pattern of eczema clear up with age, as their skins become less easily eczematized; even many patients with severe eruptions will also clear. It would only be in the very severe cases which have persisted for a long period that I would qualify my optimism.

I am sure Dr. Beare is quite right in pointing out how readily monilia invades a pre-existing eruption in the napkin area. He may remember the work of Miss M. English, who found monilia in 9 out of 30 babies with simple and mild napkin rashes and none in a series of thirty controls.³ For this reason I have taught that it is inadvisable in most cases to use antibiotics in this area, and was therefore surprised to see Dr. Beare advocating their use. For even severe napkin rashes I still use a simple routine which includes explanation and advice, the regular use of Past. Zinc. Co. and Ung. Emuls. Aquos. in equal parts, and the rinsing of the napkins, before drying, in boric acid (1 drachm to 1 pint (3.9 g. to 560 ml.) of boiling water). Very occasionally I may resort to the addition of vioform-(iodochlorhydroxyquinolin)-hydrocortisone ointment applied two or three times per day. The more powerful steroids are

significantly absorbed from the large areas of inflamed skin which may have to be treated.

In his brief account of haemangiomas Dr. Beare mentions the ulceration which may occur in the larger cavernous lesions, particularly in areas which are readily traumatized. I have been impressed by the curious degree of pain from such ulcerated areas, and, for example, when they are present in the napkin area a child will often start crying as soon as it knows the napkin is going to be changed.—I am, etc.,

Bristol 8.

ROBERT P. WARIN.

REFERENCES

- 1 Walker, R. B., and Warin, R. P., *Brit. J. Derm.*, 1956, 68, 182.
- 2 Vowles, M., Warin, R. P., and Apley, J., *ibid.*, 1955, 67, 53.
- 3 Warin, R. P., and Faulkner, K. E., *ibid.*, 1961, 73, 445.

Clofibrate and Androsterone in Hypercholesterolaemic Xanthomatosis

SIR,—The excellent results obtained by Dr. Bernard Mason and Professor C. B. Perry (9 January, p. 102) confirm the general impression of the great benefit of Atromid (clofibrate and androsterone) in patients with hypercholesterolaemic xanthomatosis. The almost universal improvement contrasts with the failure to influence other types of xanthomata. Like Mason and Perry, I have had no success in treating two patients with xanthelasma and hypercholesterolaemia. Similarly, two patients with biliary cirrhosis and extensive xanthomata have failed to lose their disfiguring skin lesions. On the other hand the two patients reported in your columns last year (17 October, p. 990) remain free of xanthomata after a further year, and the dose of Atromid is being cautiously reduced.—I am, etc.,

Dudley Road Hospital,
Birmingham 18.

B. W. ROPER.

Percutaneous Transhepatic Cholangiography

SIR,—The article by Drs. S. G. Elkington and D. C. Bernstein (19 September, p. 733) and the subsequent letter from Mr. H. A. Kidd (3 October, p. 875) on this subject has unfortunately only just come to notice out here, and I hope that it is not too late to contribute.

While fully agreeing that this is a most valuable procedure, I would put in a plea for use of the "sleeved-needle" catheter technique, as described by Shaldon and his colleagues,¹ and also by Arner and his colleagues.² It would seem better to have a soft polyethylene catheter in the liver than a long needle liable to tear that very friable organ at every respiratory excursion. Most radiologists would be more familiar with a percutaneous catheter, which has the additional advantage that it can safely be left *in situ* to permit drainage of the biliary tree as a pre-operative measure. Housset and Vantsis³ observe that decompression of the biliary system improves the vascularity of the liver and this may well improve the patient's reaction to operation. It is, of course, important to secure the catheter firmly to the skin either with a suture¹ or with a combination of Nobecutane and adhesive tape.⁴

Failure to do so adequately permits the catheter to slip out of place and bile leaks out through the liver puncture, as happened in two of my cases.⁴

Interpretation of the films requires considerable care, and it is essential, by comparison with a previous barium meal, to locate the exact site of a lesion in the common bile-duct in relation to cystic duct, duodenum, ampulla of Vater, and pancreas.

Finally, it is prudent to perform this examination only as a pre-operative measure. Although, using a catheter technique it is relatively safe to assume that failure to find bile means that the biliary tree is not dilated and, in the absence of complications from the procedure, operation may therefore not be indicated, nevertheless most surgeons would prefer to regard a case of probable obstructive jaundice as one which requires exploration. The principal purpose of this investigation, I suggest, is to assist the surgeon by providing additional pre-operative information in such a case, and other indications are in my view of most doubtful value.—I am, etc.,

P. M. BRETLAND.

British Military Hospital,
c/o G.P.O., Singapore.

REFERENCES

- 1 Shaldon, S., Barber, K. M., and Young, W. B., *Gastroenterology*, 1962, 42, 371.
- 2 Arner, O., Hagberg, S., and Seldinger, S. I., *Surgery*, 1962, 52, 561.
- 3 Housset, E., and Vantsis, G., *Presse méd.*, 1957, 65, 772.
- 4 Bretland, P. M., *J. roy. Army med. Cps*, 1964, 110, 129.

Combining the Antidepressant Drugs

SIR,—In view of the recent correspondence in the *B.M.J.* regarding the dangers of combining monoamine-oxidase inhibitors with either imipramine (Tofranil) or amitriptyline (Tryptizol, Saroten, Laroxyl) in depressive illnesses, it would seem appropriate to mention that I have just completed and am preparing for publication a special survey of more than 80 patients on such a combination. All of these patients have been seen personally by me, some over a period of many months. All had been treated previously with either a monoamine-oxidase inhibitor alone or imipramine or amitriptyline alone, and, because of their failure to respond, combined treatment was instituted. In general the dosage prescribed with combined drugs was slightly lower for each antidepressant than that prescribed when the antidepressant was used alone, although in about 15% on combined drugs full therapeutic dosage was prescribed.

In this group of patients both the nature and the incidence of side-effects when taking one antidepressant alone were very similar to those experienced on a combination of two antidepressants. In more than 80% of patients treated side-effects were either entirely absent or so mild as to be of little consequence. This was true for both single-drug treatment and combined treatment. In about 10% of cases on combined treatment this had to be discontinued or modified by reduction of dose because of the incidence of unpleasant side-effects. The corresponding figure for single-drug treatment was about 7%.

In none of the patients followed up did any disastrous or irreversible toxic effects

occur. No side-effects on combined treatment had been previously seen in patients receiving single-drug treatment.—I am, etc.,

D. R. GANDER.

Department of Psychological Medicine,
St. Thomas' Hospital,
London, S.E.1.

SIR,—Combinations of antidepressant drugs have proved to be most valuable in the treatment of depressive states and obsessional neuroses which are resistant to other therapies.

At Charing Cross Hospital extensive use has been made of these drugs in combination without dangerous side-effects, and it would be most unfortunate if the caveats of the Witts Committee were to hinder their use in clinical practice. I would support Dr. W. W. Sargent's plea (23 January, p. 251) for a rational attitude towards their continued prescription in proper dosage by psychiatrists experienced in their use.—I am, etc.,

Charing Cross Hospital,
London W.C.2.

JOHN RANDELL.

Male Breast Cancer in Klinefelter's Syndrome

SIR,—The findings of Dr. A. W. Jackson and his colleagues (23 January, p. 223) are of great interest. It would, however, have been helpful if they had included some account of the histological appearances in the non-cancerous portions of the breast parenchyma in their two cases where mastectomy was performed (Cases 1 and 3).

I have studied the histological appearances of the male breast in pubertal and senile hypertrophy; in liver disease (carcinomatosis, multilobular cirrhosis, haemochromatosis, Kinnier-Wilson disease, chronic venous congestion, and fatty change); in feminizing tumour of the adrenal cortex; after prolonged therapy with diethylstilboestrol; and in Klinefelter's syndrome. I hope to publish, in collaboration with Dr. Jean Fraser, an account of the hypertrophies of the male breast in Klinefelter's syndrome and other conditions. Acinar development and the formation of true lobules identical with those seen in the mature female breast has been seen on only one occasion after prolonged administration of diethylstilboestrol and in some, but not all, cases of *chromatin-positive* Klinefelter's syndrome.¹ The formation of acinar tissue after prolonged oestrogen therapy has been confirmed in eight further cases by other workers.²

These findings suggest that hormonal influences may play a part in the occasional development of lobular acini in the male breast in cases of Klinefelter's syndrome. This possibility could be confirmed by hormone assays in cases of *chromatin-positive* Klinefelter's syndrome which have undergone breast biopsy or mastectomy for cosmetic reasons.

If this is established it would be important also to discover whether cases of carcinoma of the male breast occurring after prolonged oestrogen therapy and in patients with Klinefelter's syndrome are ever accompanied by development of lobules of the female type. I have not seen evidence of such lobule formation in my material from cases of male breast cancer, but I have not had the oppor-