Temporary interruption of the inferior vena cava is thus unnecessary and an external bypass is avoided.

To effect a temporary portacaval bypass a side orifice is built into the lower end of the catheter with the larger lumen. This orifice can be palpated through the wall of the vena cava and temporary ligatures are applied immediately above and below this point (Fig. 2, ligatures 3 and 4). A second catheter which accurately fits this side opening (Fig. 1) can then be introduced into the distal portal vein and the proximal end inserted into the catheter with the larger lumen through a small stab wound in the wall of the vena cava overlying the side orifice. Loss of blood and air entry are prevented by occluding the small wound in the caval wall with the finger-tip until all is secure.

The proximal portal vein alone, the main hepatic artery alone, or both of these vessels, are now available for a measured blood flow to be introduced into the liver. The venous drainage of the liver is siphoned off through the catheter with the smaller lumen to a bubble oxygenator. The reservoir of the oxygenator is then connected to one or two pumps and oxygenated blood can then be perfused along either afferent route or both routes. If both are used the output from the pumps is so arranged that blood flow is in the ratio of three to one in favour of the portal vein. The double catheter is easily made, the constituent elements being ordinary polyvinyl chloride tubing or catheters glued together with the appropriate solvent (tetrahydro-furan).

This is a simple and effective method for closed-circuit perfusion of the liver. The operative technique is straightforward and the apparatus is cheap and easy to construct. The haemodynamic requirements in the experimental animal have been satisfied, and the amount of loss of perfusate to the systemic circulation has been shown by the use of radioiodine-labelled serum albumin and dyes to be negligible.

We intend to use the method for the treatment of hepatic metastases in humans in the near future, but we report it at this stage as we feel that it may be of value to other research workers in this field.

The costs of this research project to date have been borne jointly by the British Empire Cancer Campaign Research Fund and St. George's Hospital. I am indebted to numerous immediate colleagues in the general surgical and anaesthetic departments of St. George's Hospital for assistance, and notably to Mr. Duncan Forrest for much practical information and helpful advice. Fig. 1 was prepared by Miss Underhill (photographic department, St. George's Hospital), and Fig. 2 by Mr. E. Lee.

A. ELEY, F.R.C.S.,
Research Fellow, Surgical Unit,
St. George's Hospital, London.

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Medical Memoranda

Carcinoma of Breast after Adrenalectomy for Cushing's Syndrome

It now seems well established that Cushing's syndrome is sometimes associated with tumour formation in organs other than the adrenal or pituitary glands, and that in these cases Cushing's syndrome often follows an acute course and is accompanied by hypokalaemia. This association was first noted by Thorne (1952), and recent surveys of the literature by Allott and Skelton (1960) and Bagshawe (1960a, 1960b) have confirmed his opinion that the association was not fortuitous. Thorne believed that pituitary activity was the cause of the tumour formation, but because the signs of Cushing's syndrome and of tumour formation had occurred more or less simultaneously in all the cases reviewed by him, he was unable to decide whether the pituitary acted direct or through the adrenals. He rather favoured the view that the adrenals were stimulated to produce an abnormal and tumour-forming steroid. The following case seems to provide additional evidence on this point. In our case there was a continuing pituitary hyperactivity, and carcinoma of the breast developed two and a half years after the successful treatment of acute Cushing's syndrome by adrenalectomy.

CASE REPORT

The patient, a married woman, was first seen in the autumn of 1956 at the age of 42. She was deeply pigmented (Fig. 1) and acutely ill, and was found to be suffering from Cushing's syndrome associated with a severe hypokalaemia (serum potassium 1.3 mEq/l.; plasma corticotrophin, "significant amounts," more than normal; urine ketogenic steroids, 100 mg./24 hours; sella turcica not radiologically enlarged). Adrenalectomy was carried out in November, 1956. It effectively reversed all the abnormal findings, and the pigmentation disappeared (Edmunds *et al.*, 1958).

The patient remained well until the end of 1958, when pigmentation returned and she soon became even more pigmented than before. In March, 1959, the plasma corticotrophin was again estimated by Dr. Barbara Clayton and found to be greatly increased (168 i.mu/100 ml.). These signs of pituitary activity were not accompanied by any evidence of return of Cushing's syndrome or of hypokalaemia; on the contrary, the patient continued to require a daily maintenance dose of 50 mg. of cortisone. In July a pelvic examination revealed the presence of bilateral

ovarian tumours. An x-ray film of the chest showed a shadow in the anterior mediastinum, but there was still no radiological evidence of enlargement of the sella turcica. Two solid ovarian tumours, each 10 cm. in diameter, were removed at operation. Section showed undifferentiated carcinoma, and it was not clear whether the tumours were primary or secondary.

The original hormone investigations on this patient had been carried out by Professor Prunty and his colleagues, and arrangements were therefore made to transfer the patient to St. Thomas's Hospital for reassessment of her endocrine status and consideration of the possibility of hypophysectomy. Her condition was deteriorating, and by the time she was transferred a tumour had become apparent in her right breast. X-ray films showed a large mediastinal mass and bronchoscopy revealed antero-posterior compression of the trachea from a mass lying behind it. Biopsy of the breast tumour revealed a primary carcinoma, in some places showing the structure of an adenocarcinoma and in others a spheroidal-celled carcinoma similar to the ovarian tumours, which were clearly secondaries. The patient rapidly became weaker, and died at home at the end of December. It was not possible to arrange for a necropsy.

DISCUSSION

Fifty-five cases have been reported in which Cushing's syndrome has been associated with tumour formation. (The combined total of the reviews quoted above is 53, including the present case, and Christy (1961) has added two more.) The serum potassium was estimated in 39 of these cases—in 31 it was low, while in eight the lowest recorded values were above 3 mEq/l. Hypokalaemia is very rare in Cushing's syndrome without tumour formation (Bagshawe could find only two cases; and Aber and Cheetham (1961) have reported another), and this further association between Cushing's syndrome with tumour and hypokalaemia greatly strengthens the probability that in the present case Cushing's syndrome and the carcinoma of the breast were related conditions.

In studying the literature we have paid special attention to the evidence of pituitary activity. The plasma corticotrophin was estimated only in the present case and in Christy's two cases. In all three it was increased. But there was some indirect evidence that pituitary activity in the tumour cases was greater than that in uncomplicated Cushing's syndrome. Melanin pigmentation in Addison's disease is thought to be evidence of pituitary hyperfunction. Similar pigmentation is rare in Cushing's syndrome but was seen in eight of the tumour cases—six are mentioned in the above reviews and one by Sprague *et al.* (1950) and one by Norris (1938). Greater activity by the pituitary might also be inferred from indications of a higher average output of urinary steroids in the tumour cases. The urinary steroids were estimated in 12 cases either as 17-hydroxycorticosteroids or as 17-ketogenic steroids. Roughly converting the ketogenic steroids to hydroxycorticosteroids by multiplying by 0.66 (Moxham and Nabarro, 1956) gives an average for the 12 cases of 60 mg. in 24 hours (range 12–136, standard deviation 32). This may be compared with an average of 38 mg. (range 18–68, standard deviation 15) for 13 cases of uncomplicated Cushing's syndrome studied by Nabarro *et al.* (1957).

In the present case there were two periods of pituitary hyperfunction, on the evidence of increased plasma corticotrophin and pigmentation. These were at the onset of illness and during the last year of life; but for a period immediately after the adrenalectomy there was a striking reduction of pigmentation. Although no assay of plasma corticotrophin was carried out it seems likely that at this time there was a reduction of pituitary activity.

The second period of pituitary activity is the more easily explained. A number of cases have been reported in which increased corticotrophin production, pigmentation, and pituitary tumours followed within a few years the treatment of Cushing's syndrome by adrenalectomy. This has been attributed to the release of the pituitary from the inhibitory effects of the high levels of circulating hydrocortisone that existed before adrenalectomy (Montgomery *et al.*, 1959; Shrank and Turner, 1960).

Less easily explained is the reduction of pigmentation and presumably of pituitary activity that occurred in our patient in the months after the adrenalectomy. The problem is difficult, because the relative importance of the pituitary and the adrenals in initiating Cushing's syndrome is still obscure (Walters, 1953). The first period of pituitary hyperfunction in our case might be explained by saying that it was due to a net stimulating effect upon a hypersensitive pituitary, resulting from an unbalanced or abnormal production of hormones by the adrenals—this, in spite of inhibitory effects from high blood levels of hydrocortisone. Removal of the

FIG. 1

FIG. 2

FIG. 1.—Patient when first seen. Some degree of moon-face; pigmentation of face, exposed parts of neck, and knuckles. FIG. 2.—Two and a half years after adrenalectomy; the patient is even more pigmented than when first seen. Photographs are reproduced from kodachrome originals.

adrenals was therefore followed by a reduction of pituitary activity as a first effect. It is possible, however, that the phase of depigmentation was only coincidentally related to the adrenalectomy, and represented a natural remission of pituitary hyperfunction. In Bagshawe's personal case a deep-brown pigmentation of the exposed skin appeared first and then faded, to be followed later by Cushing's syndrome and carcinoma of the lung. Remissions occurred in the cases of Cushing's syndrome associated with thymic neoplasms described by Sprague *et al.* (1950) and Anderson and Haymaker (1944). A remarkable case of cyclical remissions in Cushing's syndrome has recently been described by Aber and Cheetham (1961). During the attacks there was a high level of excretion of urinary steroids and severe hypokalaemia. The patient died during an attack, but, surprisingly in view of the hypokalaemia, no tumour was found at necropsy.

It seems very likely that carcinoma did not develop in our patient until the second period of pituitary hyperactivity, and some long time after adrenalectomy. We had read Thorne's paper at an early stage in our investigations and were aware of the further sinister associations of Cushing's syndrome with hypokalaemia. Repeated clinical and radiological examinations were made, seeking evidence of tumour formation; also a careful search when the abdomen was opened to carry out adrenalectomy. Nothing, however, was found until the last year of the patient's life. If we accept a causal relationship between Cushing's syndrome and the development of carcinoma of the breast, the sequence of events strongly suggests that the pituitary was exercising a direct carcinogenic action.

Our thanks are due to Professor F. T. G. Prunty and his colleagues for help with this case and for permission to use the notes taken at St. Thomas's Hospital.

A. W. B. EDMUNDS, M.B., M.R.C.P., M.R.C.P.Ed.,
Physician,

K. C. McKEOWN, M.Ch., F.R.C.S., F.R.C.S.Ed.,
Senior Surgeon,

Friarage Hospital, Northallerton, and the Memorial Hospital,
Darlington.

P. N. COLEMAN, M.B., Ch.B.
Pathologist, Friarage Hospital, Northallerton.

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Dissolution of Cystine Calculi

The purpose of this paper is to report a case in which cystine calculi were dissolved by deliberate increase in urine flow both by day and by night. This form of treatment was suggested by Dent and Senior (1955); they thought that a daily output of 3 litres of urine of normal pH would hold the output of cystine of the average cystinuric in true solution and expose stones to the solvent action of a urine undersaturated with cystine. They emphasized that the urinary output must be equally divided over the 24 hours in order to avoid supersaturation of the night urine with cystine. Harris and Robson (1957), however, thought that it was extremely unlikely that stones of any significant size would be dissolved by this form of treatment, and indeed there is a lack of reported successes.

CASE REPORT

A boy of 11 years was admitted to hospital in May, 1957, with a 3½-months history of attacks of abdominal pain, on one occasion associated with haematuria. Examination at that time disclosed some tenderness in the right side of his abdomen, and a straight x-ray film showed numerous calculi in the left renal area. Cystine crystals were found in his urine, and an I.V.P. showed a left hydronephrosis and a non-functioning right kidney. He then passed a stone which analysis proved to contain cystine, and a subsequent I.V.P. showed a normal right kidney and a persisting hydronephrosis on the left side. His daily excretion of cystine varied between 700 and 900 mg., which indicated that he was an average cystinuric. His blood-urea was 28 mg./100 ml. and his electrolytes were normal. His serum calcium and phosphorus, creatinine clearance test, plasma proteins, response to the ingestion of ammonium chloride, and his alkaline phosphatase were all normal.

On his normal intake of fluids his average 24-hour urine excretion was 1,220 ml. On forced fluids with no night waking his urine output was 3,700 ml. in 24 hours, but this was not equally divided over the day, and it was only with

FIG. 1.—Multiple stones present in June, 1957, before treatment.

The Radcliffe Infirmary Diabetic Clinic has issued a fourth edition of its *Notes for Patients*, which is a booklet designed to help the diabetic patient to adjust his life and habits to the restrictions imposed by his disease. It has been compiled with the help of Dr. C. M. Fletcher, Dr. J. C. Pease, Dr. D. A. Pyke, Dr. G. E. Honey, and Dr. A. M. Cooke.