THE PRE-OPERATIVE AND POST-OPERATIVE CARE OF PATIENTS RECEIVING CORTISONE OR OTHER STEROID THERAPY

By ROBERT R. DE MOWBRAY, D.M., M.R.C.P.

Senior Medical Registrar, St. Bartholomew's Hospital, London

Surgical operations may be hazardous on patients who are being treated with steroid hormones or who have recently received such therapy. This is a problem which is likely to occur more frequently now that cortisone and the Δ_1 -steroids, prednisone and prednisolone have been made generally available. The situation may arise in one of two ways. First, the patient may be receiving small (physiological) doses of cortisone as replacement therapy for adrenal insufficiency, due either to Addison's disease, to panhypopituitarism or to total adrenalectomy. Secondly, patients may be receiving large (pharmacological) doses of cortisone or Δ_1 -steroids for the treatment of such conditions as rheumatoid arthritis, collagen disease or ulcerative colitis. Such patients may have to undergo surgical operations on account of some incidental disease or for specific complications of steroid therapy such as perforation of a peptic ulcer. While they are receiving steroid hormones in large doses, and for some months or a year or more after steroid therapy has been discontinued, these patients are suffering from potential adrenal insufficiency due to suppression of endogenous adrenal cortical function. Careful pre-operative assessment and management of patients with actual or potential adrenal insufficiency is of vital importance. Post-operative care is but a continuation of the pre-operative regime; to postpone treatment until after the operation may be to court disaster, for it is often difficult to resuscitate the patient once profound adrenal failure has supervened.

Physiological Background

The Adrenal Response to Surgical Stress. It has been known for many years that patients with adrenal insufficiency are incapable of responding adequately to surgical operations. This applies even to minor procedures such as dental extractions. Thorn (1951) stated that no major surgical operation had been performed success-

fully in a patient with classical signs and symptoms of Addison's disease until deoxycortone acetate was introduced in 1938. The role of the adrenal cortex in response to stress was elaborated by Selye from 1936 onwards and since then evidence of increased adrenal cortical activity has been demonstrated during and after surgical operations on otherwise healthy individuals. This is shown by the fall in the eosinophil count in the blood (Laragh and Almy, 1948; Roche *et al.*, 1950; Hardy, 1955), by the increase in plasma levels of 17-hydroxycorticoids (Tyler *et al.*, 1953, 1954; Sandberg *et al.*, 1954; Franksson *et al.*, 1954, 1955; Elman *et al.*, 1955; Hammond *et al.*, 1956; Steenburg *et al.*, 1956; Helmrich *et al.*, 1957; Virtue *et al.*, 1957) and by the increased output of corticoids and 17-ketosteroids in the urine (Venning *et al.*, 1944; Browne and Venning, 1947; Forbes *et al.*, 1947; Thorn *et al.*, 1953; Cope and Hurlock, 1954; Moncrieff *et al.*, 1954; Tompsett and Smith, 1954; Hardy, 1955; Moore *et al.*, 1955; Hammond *et al.*, 1956; Jepson *et al.*, 1956). The adrenal cortical response to stress is thought to be due to stimulation of the hypothalamo-hypophyseal pathways, resulting in an increased output of corticotrophin (ACTH) by the anterior lobe of the pituitary gland (Thorn *et al.*, 1953). Increased corticotrophic activity has in fact been demonstrated in the blood after operations (Taylor *et al.*, 1949; Bornstein and Trehwella, 1950).

Suppression of Adrenal Cortical Function by the administration of Steroid Hormones. The administration of steroid hormones leads to suppression of endogenous adrenal cortical activity. This is shown by the occurrence of symptoms of adrenal insufficiency after sudden withdrawal of the hormone, by the fall in output of 17-ketosteroids in the urine during steroid therapy, and by atrophy of the adrenal cortex and depletion of its lipid at autopsy. The capacity of the adrenal cortex to respond to stimulation by

corticotrophin is also impaired by intensive steroid therapy. This accounts for the poor response to surgical stress which patients are liable to show after prolonged and intensive administration of steroid hormones (Sprague *et al.*, 1950; Thorn *et al.*, 1953). The risk is probably no less in patients receiving corticotrophin (ACTH) than in those who are being treated with cortisone (Salassa *et al.*, 1953; Hayes, 1956). Prolonged treatment with corticotrophin leads to degeneration and later hyaline changes in the basophil cells of the anterior pituitary lobe, similar to those induced by cortisone therapy, together with basophil stippling of the chromophobe cells (Golden *et al.*, 1950; Bennett, 1954). These changes suggest that the administration of either cortisone or corticotrophin interferes with the release of endogenous corticotrophin by the anterior pituitary lobe. Furthermore, the increased secretion of adrenal steroids under the influence of exogenous corticotrophin is likely to depress the output of endogenous corticotrophin. However, adrenal insufficiency resulting from withdrawal of corticotrophin therapy is likely to be less prolonged than after withdrawal of cortisone (Thorn *et al.*, 1953). It is possible that the operative risk will prove to be greater in patients receiving treatment with prednisone or prednisolone than in those being treated with cortisone, since the former steroids are metabolized more slowly (Slaunwhite and Sandberg, 1957) and are more potent in inhibiting the output of steroids in the urine than are equivalent doses of cortisone (Nabarro *et al.*, 1955; Spence *et al.*, 1956).

Post-operative Collapse in Patients Receiving Steroid Therapy

The risk of operating on patients with Addison's disease has already been emphasized and it still exists in patients who are receiving replacement therapy, unless the dose of cortisone is substantially increased over the period of the operation. The same applies to patients with adrenal insufficiency secondary to hypopituitarism (Ingraham *et al.*, 1952; Kyle *et al.*, 1953; Troen and Ryneason, 1955). The operative risk is less easily appreciated in patients who are receiving pharmacological doses of corticotrophin or steroid hormones, for such patients may show some of the features of Cushing's syndrome, as a result of excessive endocrine therapy, and yet may fail to produce an adequate adrenal response to surgery or other forms of stress (Thorn *et al.*, 1953).

Most authors stress the dangers of operating on patients during or after pharmacological steroid therapy, yet, as Salassa *et al.* (1953) point out, many thousands of these patients must have undergone

surgical operations and comparatively few disasters have been reported. The writer has succeeded in collecting from the literature only 33 cases of post-operative shock in patients who have received corticotrophin or steroid therapy in pharmacological doses. Fifteen of these cases were reported by Hayes (1956) and were drawn from a group of 28 patients who underwent surgical operations during or after endocrine therapy; that is to say, the incidence of post-operative shock in patients who had received corticotrophin or steroid therapy in pharmacological doses was just over 50 per cent. In contrast, there was no episode of post-operative shock among 25 patients who were suffering from diseases amenable to steroid therapy but who had not been treated with steroid hormones. Five of the patients developed post-operative shock at intervals of 3 to 24 months (mean 11 months) after steroid therapy had been withdrawn. One patient collapsed after an operation while still receiving corticotrophin (ACTH) in unchanged doses and post-operative shock occurred in another patient from whom corticotrophin had been withdrawn two months previously. Slaney and Brooke (1957) reported seven cases, of which six occurred in patients with ulcerative colitis. These patients had received total doses of 2 to 9 g. of cortisone over periods of 2 to 6 weeks. Three of their patients had no operative cover with steroid hormones, although two of them had received corticotrophin for 5 to 14 days before operation, and all three died in post-operative shock. The other four patients received extra doses of cortisone during the operative period, and although they all collapsed after operation they were resuscitated by further doses of cortisone or intravenous hydrocortisone; one of them died after a second operation which was complicated by a burst wound. Slaney and Brooke subsequently performed ten operations on eight patients with ulcerative colitis who had previously been treated with steroid hormones; in all these patients the operation was systematically covered with intensive doses of intramuscular cortisone and intravenous hydrocortisone and no post-operative complications ensued. Nicholas *et al.* (1955) reported two cases (one of them fatal), Salassa *et al.* (1953) reported two fatal cases and Fraser *et al.* (1952), Lewis *et al.* (1953) reported one fatal case each of post-operative shock, after total doses of 8 to 14 g. of cortisone or more over periods of four months to five years. Allanby (1957) recorded a similar case after a total dose of 560 mg. of prednisolone over a period of four weeks. Forbes (1952) reported death soon after a partial gastrectomy in a patient with a gastric ulcer who had recently been given cortisone, 100 mg. daily for three weeks, but he did not describe

the mode of death. Kern (1957) mentions a patient with rheumatoid arthritis who died of adrenal failure 24 hours after the incision of an infected olecranon bursa under local anaesthesia. Only two of these last nine patients received adequate doses of steroid over the operative period (Nicholas *et al.*, 1955). In three of the cases steroid therapy had been discontinued two days, four days and five months respectively before operation (Fraser *et al.*, 1952; Allanby, 1957; Salassa *et al.*, 1953). The possibility of adrenal failure was apparently considered in only four of the patients and they were given additional cortisone intramuscularly and hydrocortisone intravenously (Salassa *et al.*, 1953; Nicholas *et al.*, 1955). Thus in 11 out of 17 cases the outcome was fatal, only one of these patients having had adequate steroid therapy over the operative period. Harnagel and Kramer (1955) reported acute adrenal failure in a man aged 21 years with spondylitis, 12 hours after manipulation of the spine under thiopentone anaesthesia. The patient had received a total of 1.9 g. cortisone over the previous month, the last dose being given 18 hours before the manipulation. The patient was resuscitated only after four days' intensive therapy with intravenous corticotrophin and cortical extract and intramuscular cortisone. The 17-ketosteroid output in the urine was still only 2.2 mg. per 24 hours at the end of this time. Hayes (1956) does not mention the outcome of his 15 cases but Hayes and Kushlan (1956) describe four patients (presumably included in the same series) all of whom recovered with the help of additional corticotrophin over the period of the operation.

The writer has recently had experience of a man aged 61 years with rheumatoid arthritis who had been receiving steroid therapy for 2½ years (cortisone 75 mg. daily for the first year and subsequently prednisone 25 mg. daily). After 11 months' treatment an arthrodesis of the right ankle and foot was performed uneventfully. After a total of 26 months he developed bronchopneumonia, at which time he ceased to take his prednisone tablets; he developed anuria and adrenal failure but was revived with 100 mg. intravenous hydrocortisone and oral cortisone 150 mg. daily. Six weeks later amputation of the right leg was performed on account of a persistent discharging sinus in the right ankle. Although he was given corticotrophin zinc 80 units daily intramuscularly for three days before operation, he developed post-operative pneumonia and signs of adrenal insufficiency. He eventually recovered with the aid of antibiotics, 200 mg. intravenous hydrocortisone, prednisone 40 mg. daily and the continued administration of corticotrophin zinc

80 units daily. The corticotrophin was then gradually withdrawn and the prednisone gradually reduced to his usual dose of 25 mg. daily.

Hayes (1956) points out that the response to surgery cannot reliably be predicted from the total dosage, from the duration of therapy or from the interval between the conclusion of therapy and the operation. Post-operative collapse occurred at intervals of up to two years after the end of therapy in his cases and Salassa *et al.* and Slocumb *et al.* (1957) also consider that the danger may exist for as long as two years after the withdrawal of corticotrophin or steroid hormones. Obviously the degree and duration of adrenal suppression varies tremendously from patient to patient. As judged by the fall in eosinophil count and the increase in steroid concentrations in the blood and urine in response to exogenous corticotrophin, pituitary adrenal inhibition may persist for anything from two to 90 days after the withdrawal of steroid therapy (Boland and Headley, 1951; McIntosh and Holmes, 1951; Ragan, 1953; Thorn *et al.*, 1953; Eik-Nes *et al.*, 1955).

Bennett (1954) found that the weights of human adrenal glands at autopsy were significantly reduced if cortisone had been given up till the time of death and for more than five days altogether but the adrenal cortex was not atrophic if cortisone had been discontinued more than 20 days before death. However, the size and histological appearances of the glands do not necessarily reflect their functional activity. Assessment of the adrenal cortical response to corticotrophin during life cannot be entirely relied upon to predict or exclude the likelihood of post-operative collapse. Therefore it is safest to give full supportive endocrine therapy before, during and after operation in all patients who have been treated with corticotrophin or steroid hormones, at any rate within the previous two years.

Surgical Complications of Peptic Ulcer in Patients Receiving Corticotrophin and Steroid Therapy

This problem deserves special consideration, for the physician and the surgeon are faced with the dilemma of a patient in whom peptic ulceration and its complications may be the direct result of corticotrophin or steroid therapy, yet who will temporarily require even higher doses of these hormones in order to respond to the stress of perforation or haemorrhage and their respective surgical treatment. The writer has collected from the literature 21 cases of perforation, and 25 cases of haemorrhage complicating peptic ulcers, and three cases in which both perforation and haemorrhage occurred. In eight out of the 14 cases of perforation and in seven out of 12 cases of

haemorrhage in which details are available there was no history of peptic ulcer before steroid therapy was started. In 14 cases in which details are available perforation occurred after periods of 5 to 37 days (mean 20 days) of treatment with corticotrophin or steroid hormones or both. In 16 cases haemorrhage occurred after periods of nine days to one year (mean six months) of treatment. Thus perforation has occurred consistently within 1 to 5 weeks of therapy and haemorrhage after variable and often lengthy periods of treatment. This suggests that perforation is a specific complication of steroid therapy while in many cases the haemorrhage may have been incidental and might well have occurred in the absence of treatment with these hormones. In 14 out of 17 cases the perforation was treated surgically, in one case it was treated conservatively and in two others it was found unexpectedly at autopsy. Uneventful recovery followed in the patient treated conservatively and in all except one of the patients treated surgically. One of the patients reported by Smyth (1951) died after operation. In four cases the symptoms and signs of perforation were masked. In only two of the case reports it stated that additional steroid therapy was given over the operative period (Fentress *et al.*, 1956; Hess and Macpherson, 1957). Of 14 patients with haemorrhage 13 were treated conservatively and four of these died; one patient was treated surgically but was found to have multiple erosions in the stomach and intestines and died soon after operation (Allanby, 1957). In at least six of these patients steroid therapy was continued despite the occurrence of bleeding though the doses were gradually reduced.

Judging from this analysis of the literature it would appear that surgical treatment of a perforated peptic ulcer is a relatively safe procedure in a patient receiving steroid therapy. This may be due to the fact that the perforation has in most cases occurred within 3 to 5 weeks' treatment, which may not have been long enough to lead to profound suppression of pituitary-adrenal function.

The writer has had recent experience of perforated peptic ulcer in two patients receiving steroid therapy. One patient was a man aged 49 years with rheumatoid arthritis who had received a total of 300 mg. of hydrocortisone by intra-articular injection followed by a total of approximately 1 g. of prednisolone by mouth during the course of six weeks. The perforation was sutured without additional steroid cover and uneventful recovery ensued. The other patient was a woman aged 45 years with exophthalmic ophthalmoplegia who had received 200 mg. cortisone daily by intramuscular injection for 17 days previously.

In this case cortisone was continued in the same dosage over the operative period and hydrocortisone was given by intravenous infusion.

In spite of the favourable outcome of surgical treatment in most of these cases the writer would still prefer to give additional steroid therapy over the operative period in every case. The situation is less clear-cut in the case of gastro-intestinal haemorrhage arising during steroid-therapy. If conservative management is decided upon, it is necessary to weigh up the need for increased doses of steroid, to meet the stress of haemorrhage (Ward *et al.*, 1953) against the risk of aggravating the ulcer still further. If surgical management is decided upon, increased doses of steroids will again be required and, in the absence of previous evidence of peptic ulceration, there is the risk of operating on a patient with multiple acute peptic erosions or haemorrhagic gastritis, as in the case reported by Allanby (1957).

The writer has had recent experience of a male patient aged 52 years who had been treated with a total of approximately 25 g. of cortisone over a period of eight months, followed by a total of approximately 5 g. of prednisolone over a period of six months and was admitted to hospital with massive haematemesis and melaena. This patient had had no previous ulcer symptoms whatsoever and the writer hesitated to advise surgical treatment in view of the risks of adrenal failure and the possibility of multiple peptic erosions. The patient improved temporarily with intravenous hydrocortisone but had repeated massive haemorrhages and died 24 hours after admission. At autopsy a subacute duodenal ulcer was found which had eroded the superior pancreaticoduodenal artery. In retrospect it would have been preferable to administer more intensive steroid therapy and to recommend surgical interference as soon as the patient's general condition was adequately restored.

Details of Pre-operative and Post-operative Management

The occasional disasters which follow surgical operations in these patients could be reduced dramatically by fully acquainting the patient and all who are responsible for his care with the fact that he is suffering from adrenal insufficiency or has been treated with steroids and with the necessity of taking certain precautions, should the need for surgery arise. This can be done most conveniently, as recommended by Forsham and Thorn (1955) and by Slocumb *et al.* (1957), by giving the patient a card, to be carried at all times and bearing his name and address, the name and address of his private doctor and con-

sultant physician, the nature of his disease and the dose of steroid hormone which he is receiving. The patient should always carry a supply of cortisone tablets with him and instructions should be included on the card to give him 100 mg. cortisone immediately in case of emergency and to notify his private doctor or physician at once. The patient or his relatives should be instructed to present his card to the surgeon or dental surgeon in case of accident or impending operation or dental extraction so that the necessary pre-operative therapy can be undertaken. Now that steroid hormones are likely to be more generally used a specific enquiry as to present or past treatment with these agents should become an indispensable item in the taking of all patients' histories.

In view of the difficulty of predicting which patients are likely to develop adrenal failure after operation, it is wise to give additional doses of steroids in all cases over the operation period, regardless of the duration of steroid therapy and of the doses previously administered. The scheme outlined by Thorn *et al.* (1953) is to be recommended and is applicable to all patients undergoing major surgery, whether the patient is suffering from Addison's disease or has undergone total adrenalectomy or is receiving pharmacological doses of steroid hormones.

SCHEME OF PRE-OPERATIVE AND POST-OPERATIVE THERAPY (Thorn *et al.*, 1953)

Pre-operative: Cortisone, 100 mg. i.m.i. 12 hr. pre-op; 100 mg. i.m.i. 2 hr. pre-op.

During operation and for four to six hours after operation: Hydrocortisone, 10 mg. per hour by intravenous infusion, in dextrose or dextrose saline solution.

Post-operative during first 24 hours: Cortisone, 50 mg. six-hourly i.m.i.

Days 2 and 3: Cortisone, 50 mg. eight-hourly i.m.i.

Days 4 and 5: Cortisone, 50 mg. 12-hourly i.m.i.

Day 6: Cortisone, 25 mg. six-hourly by mouth.

Day 7 onwards: Reduce cortisone gradually to 12.5 to 25 mg. b.d. (plus deoxycortone acetate, 1 mg. daily i.m.i., in cases of Addison's disease and post-adrenalectomy state only).

In the case of emergency operations this scheme must be instituted immediately and the two pre-operative doses of cortisone should be combined as a single injection of 200 mg. before operation. In the case of elective surgery the operation should, if possible, be postponed until a physician with special experience of this problem has been consulted. In patients who are receiving or have received steroid therapy a preliminary course of corticotrophin (ACTH) should be given in order to improve adrenal cortical function and the capacity to respond to stress. Ideally this should be controlled by estimations of the output of 17-ketosteroids and/or 17-hydroxysteroids in the urine. To achieve maximal stimulation of the

adrenal cortex, 20 units of corticotrophin should be given by intravenous infusion over a period of eight hours each day, or Acthar-gel or corticotrophin zinc should be given intramuscularly in doses of 40 units 12 hourly. This should be continued for one week, for although some patients on steroid therapy may respond to three days' stimulation with corticotrophin others may require four to six days' stimulation (Engleman *et al.*, 1953). (Thorn *et al.*, 1953.) The dose of cortisone should be reduced gradually by 12.5 to 25 mg. every second day during the administration of corticotrophin (Thorn *et al.*, 1953). The administration of corticotrophin is only an adjunct to the pre-operative preparation of the patient and is not a substitute for cortisone and hydrocortisone, which must still be given as outlined over the operative period.

The writer has had recent experience of an asthmatic patient who had been receiving prednisone in doses of 30 mg. daily for one year. Prednisone was gradually withdrawn during the next two months and was followed by corticotrophin zinc 185 units over eight days. Three weeks later the output of 17-ketosteroids in the urine was only 1 mg. daily but was raised to 14.5 mg. daily by the administration of corticotrophin-zinc within 48 hours, in spite of the continued administration of 30 mg. prednisone; when the prednisone was gradually withdrawn and the corticotrophin was discontinued after a total of 10 days the 17-ketosteroid output in the urine fell rapidly again to between 2 and 3 mg. daily.

Thus treatment with corticotrophin does not immediately restore the suppressed adrenal cortex to normal nor is the response always permanent, and its effect must be gauged by estimation of steroids in the urine, the results of which cannot be obtained within less than 48 hours. For this reason corticotrophin must not be relied on as a sole means of pre-operative preparation, though it is undoubtedly beneficial.

The reason for giving cortisone acetate intramuscularly over the operation period is that its absorption is slow and prolonged by this route and the injection thus acts as a depot; it begins to act in 3 to 4 hours, reaches its peak effect in 8 to 12 hours and continues for 24 hours or more (Thorn *et al.*, 1953). For the same reason this method of administration is inadequate in itself to counter the acute stress of the actual operation; the latter must be met with an intravenous infusion of hydrocortisone which acts rapidly but ceases to be effective after about 4 hours. Cortisone acetate is absorbed more rapidly from the oral than from the intramuscular route, and exerts its maximal effect in 4 to 8 hours (Thorn *et al.*, 1953), but its use is, of course, limited to the post-operative period

when the patient is able to take food and therapy by mouth.

Intravenous Therapy. Saline solutions should be used with particular caution for the purpose of intravenous therapy since patients who have already been treated with cortisone or corticotrophin may be suffering from excessive retention of sodium and water. They may also be depleted by potassium if they have been receiving large doses of cortisone or corticotrophin over long periods. Potassium supplements may therefore be necessary.

Other Measures. The administration of corticotrophin or steroid hormones is liable to induce a negative nitrogen balance (Sprague *et al.*, 1950; Thorn *et al.*, 1953). This will exaggerate the negative nitrogen balance which is liable to follow any surgical operation. The loss of nitrogen resulting from treatment with corticotrophin or cortisone can be compensated for by doubling the intake of calories and protein (Pearson *et al.*, 1949) by the administration of 4 to 12 g. of potassium chloride daily (Kinsell *et al.*, 1952; Whitney and Bennett, 1952) and by androgen therapy. The administration of testosterone propionate 25 mg. daily by intramuscular injection has been shown to reverse the negative nitrogen balance induced by 200 mg. of cortisone daily (Sprague, 1951).

Other Post-operative Complications

Infections. Treatment with corticotrophin or steroid hormones increases the susceptibility of patients to infections. The inflammatory response may be masked even though the infection continues unabated (Thorn *et al.*, 1953). Adrenal failure is liable to supervene unless the doses of steroids are increased (Page, 1954; Jacobs and Clifford Rose, 1955; Shaper and Dyson, 1955; Allanby, 1957).

Antibiotic therapy is therefore desirable over the period of operation, and provided this is given in adequate doses the risk of the increased doses of steroid hormones will be met (Thorn *et al.*, 1953).

Delayed Healing of Wounds. This complication is not as common or as serious as was originally feared. In the early days of treatment with corticotrophin and cortisone delayed healing was reported in a few instances in biopsy wounds, incisions into abscesses and bed sores (Ragan *et al.*, 1949; Plotz *et al.*, 1950 a.c.; Behrman and Goodman, 1950; Creditor *et al.*, 1950; Videback *et al.*, 1950; Levin *et al.*, 1953). Delayed healing of wounds and fractures has also been reported in numerous animal experiments but some workers have not obtained this effect. It is clear that there is considerable variation in the effects on different species and the effect is also dependent upon the dose of hormones used and upon the state of

nutrition (Ragan *et al.*, 1953). In many of the animal experiments the doses were out of all proportion to those used clinically. Ragan (1953) found that healing was delayed in open granulating wounds and in wounds with intestinal anastomoses when cortisone was given in doses of more than 100 mg. daily; on doses of less than 100 mg. daily healing was only slightly prolonged and this was overcome by leaving the sutures in place for a slightly longer period than usual. Thorn *et al.* (1953) state that serious interference with healing rarely occurs unless the doses of steroid are unduly high (more than 150 mg. cortisone daily) and excessively prolonged and unless the intake of protein is inadequate.

Thrombo-embolic Complications. Views as to the influence of steroid therapy on thrombo-embolism are controversial. Cosgriff *et al.* (1950, 1951) originally reported that the clotting time of venous blood was shortened and recorded 48 episodes of thrombosis and embolism in 700 patients treated with corticotrophin or cortisone; this was a higher incidence than would have been expected without the use of endocrine therapy. Coste *et al.* (1951) reported five similar cases. Subsequent workers have not confirmed these results. Fahey (1951) found no significant effects on the clotting time. Variable effects on the clotting mechanisms of the blood were reported by Monte *et al.* (1950), Smith *et al.* (1950) and Margulis *et al.* (1950). Russek *et al.* (1954) found no instance of thrombo-embolic complications among 100 patients with cardiovascular disease, including patients with angina pectoris and previous cardiac infarction. Allanby (1957) states that the incidence of thrombo-embolism amongst patients treated with corticotrophin and steroid hormones at Guy's Hospital 'has not appeared abnormal.' Hume and Moore (1951) considered that thrombophlebitis was perhaps more liable to follow withdrawal of steroid therapy than it was to occur during treatment; they suggested that the general liability of surgical patients to post-operative venous thrombosis might be related to the falling off of adrenal cortical activity after the increased secretion during the operation period. Steroid therapy might therefore discourage rather than provoke thrombo-embolic complications. Indeed, striking subjective and objective improvement has been reported in patients with thrombophlebitis within 24 hours' treatment with corticotrophin or cortisone (Hume and Moore, 1951; McGraw *et al.*, 1952; Flickinger and Henderson, 1956).

Complications in Ulcerative Colitis. Instances of perforation of the colon have been reported in patients with ulcerative colitis during the administration of steroid therapy. (Tulin and Almy, 1952; Kirsner and Palmer, 1951; Texter *et al.*,

1953; Hayes and Kushlan, 1956). Since this complication is liable to occur in the absence of steroid therapy, it is not necessarily justifiable to attribute it to the use of hormones. On occasions the colon is said to have disintegrated during manipulation in patients who have been treated with steroids (Larkin and Flannery, 1953; Brooke, 1956).

Some surgeons may therefore be disinclined to use endocrine therapy when surgery is contemplated for patients with ulcerative colitis. Unfortunately, many of their patients are likely to have been treated with steroids in the past and they may be incurring a serious risk unless they cover their operations in such patients with additional doses of cortisone and intravenous hydrocortisone. Slaney and Brooke (1957), who were formerly disinclined to use steroid cover, have been forced to reverse their policy. They point out that the mortality of surgically treated patients who have previously received steroid therapy was 32 per cent. in Truelove and Witts' series (1955), as compared with a surgical mortality of 10 to 12 per cent. in the pre-cortisone era (Brooke, 1956; Swinton, 1956), but they suggest that adrenal insufficiency due to previous steroid therapy may have played a part in the high post-operative death rate reported by Truelove and Witts.

Summary

Surgical operations are hazardous on patients who are being treated with corticotrophin (ACTH) or steroid hormones, or who have previously received such treatment. This risk applies both to patients who are taking small replacement doses of cortisone for the treatment of adrenal insufficiency due to Addison's disease, hypopituitarism or previous adrenalectomy and to patients who have been given pharmacological doses of corticotrophin or steroids for the treatment of such condition as rheumatoid arthritis, collagen diseases and ulcerative colitis. In all such patients endogenous cortical adrenal function and the capacity to respond to surgical stress are absent or impaired. Post-operative adrenal failure is liable to occur and is often fatal, unless the doses of hormone are increased over the period of the operation. The risk applies to minor as well as major operations and may still exist as long as two years after steroid therapy has been withdrawn.

Although comparatively few cases of post-operative adrenal failure have been reported after pharmacological steroid therapy, there is no reliable means of predicting which patients are likely to be susceptible. Therefore, full supportive endocrine therapy, with additional doses of intramuscular cortisone acetate and intravenous hydrocortisone, should be given over the period of the

operation in all cases. In the case of elective surgery the operation should be deferred until an expert physician has been consulted and preliminary stimulation with corticotrophin has been carried out.

Patients who require operations for perforated or bleeding peptic ulcers also need additional doses of steroids, even though these complications may be the direct result of steroid therapy.

An enquiry as to present or past steroid therapy should become a routine item in the taking of case histories and every patient receiving such treatment should carry written information as to diagnosis and steroid dosage, with instructions to present this information immediately to the surgeon attending him.

Sodium retention and potassium depletion are liable to occur and the usual post-operative negative nitrogen balance is liable to be accentuated. Avoidance of excessive sodium chloride, an increased intake of calories, protein and potassium and, if necessary, the administration of testosterone, will obviate the semetabolic disturbances.

Susceptibility to infections is increased and antibiotic cover is always desirable.

Healing of wounds seldom presents any serious problem and there is little evidence of an increased tendency to thrombo-embolic complications.

BIBLIOGRAPHY

- ALLANBY, K. D. (1957), *Lancet*, **i**, 1104.
 BEHRMAN, H. T., and GOODMAN, J. J. (1950), *J. Amer. med. Ass.*, **144**, 218.
 BENNETT, W. A. (1954), *J. Bone Jt. Surg.*, **36A**, 867.
 BOLAND, E. W., and HEADLEY, N. E. (1951), *Calif. Med.*, **74**, 416.
 BORNSTEIN, J., and TREWHILLA, P. (1950), *Lancet*, **ii**, 678.
 BROOKE, B. N. (1956), *Ibid.*, **ii**, 532, 1175.
 BROWNE, J. S. C., and VENNING, E. H. (1947), *Trans. Ass. Amer. Phys.*, **60**, 16.
 COPE, C. L., and HURLOCK, B. (1954), *Clin. Sci.*, **13**, 69.
 COSGRIFF, S. W. (1951), *J. Amer. med. Ass.*, **147**, 924.
 COSGRIFF, S. W., DIEFENBACH, A. F., and VOGT, W. (1950), *Amer. J. Med.*, **9**, 752.
 COSTE, F., GALURICHE, P., PIGNET, B., DELBARRA, F., and LAURENT, F. (1951), *Rev. rhum.*, **18**, 189.
 CREDITOR, M. C., BEVANS, M., MUNDY, W. L., and RAGAN, C. (1950), *Proc. Soc. exp. Biol. (N.Y.)*, **74**, 245.
 EIK-NES, K., SANDBERG, A. A., MIGCON, C. J., TYLER, F. M., and SAMUELS, L. T. (1955), *J. clin. Endocr.*, **15**, 13.
 ELMAN, R., WEICHELBAUM, T. E., MONCRIEFF, J. C., and MARGRAF, H. W. (1955), *Arch. Surg. (Chicago)*, **71**, 697.
 ENGLEMAN, E. P., KRUPP, M. A., JOHNSON, H. P., WELSH, J. E., WRENN, H. T., and KING, W. R. (1953), *Arch. intern. Med.*, **91**, 1.
 FAHEY, J. L. (1951), *Proc. Soc. exp. Biol. (N.Y.)*, **77**, 491.
 FENTRESS, V., FIRNSCHILD, P., and REVENO, W. S. (1956), *New Engl. J. Med.*, **254**, 657.
 FLICKINGER, F. M., and HENDERSON, I. W. D. (1956), *Surg. Gynec. Obstet.*, **102**, 66.
 FORBES, J. (1952), *Lancet*, **ii**, 555.
 FORBES, A. P., DONALDSON, E. C., REIFENSTEIN, E. C., and ALBRIGHT, F. (1947), *J. clin. Endocr.*, **7**, 264.
 FORSHAM, P. H., and THORN, G. W. (1955), 'Textbook of Endocrinology,' ed. R. H. Williams, Philadelphia, W. B. Saunders Co., ch. 4.
 FRANKSSON, C., and GEMZELL, C. A. (1955), *J. clin. Endocr.*, **15**, 1069.
 FRASER, C. G., PREUSS, F. S., and BIGFORD, W. D. (1952), *J. Amer. med. Ass.*, **149**, 1542.

- GOLDEN, A., BONDY, P. K., and SHELDON, W. H. (1950), *Proc. Soc. exp. Biol. (N.Y.)*, **74**, 455.
- HAMMOND, W. G., ARONOW, L., and MOORE, F. D. (1956), *Ann. Surg.*, **144**, 715.
- HARDY, J. D. (1955), 'Surgical Physiology of the Adrenal Cortex,' C. C. Thomas, Springfield.
- HARNAGEL, E. E., and KRAMER, W. G. (1955), *J. Amer. med. Ass.*, **158**, 1518.
- HAYES, M. A. (1956), *Surgery*, **90**, 945.
- HAYES, M. A., and KUSHLAN, S. D. (1956), *Gastroenterology*, **30**, 75.
- HELENRICH, M. L., JENKINS, D., and SWAN, M. (1957) *Surgery*, **41**, 895.
- HESS, E. V., and MACPHERSON, M. E. (1957), *Brit. med. J.*, **i**, 271.
- HUME, D. M., and MOORE, F. D. (1951), *Proc. 2nd clin. ACTH Conf.*, ed. J. R. Mote, London, J. & A. Churchill Ltd., **2**, 289.
- INGRAHAM, F. D., MATSON, D. D., and McLAURIN, R. L. (1952), *New Engl. J. Med.*, **246**, 568.
- JACOBS, J. H., and CLIFFORD ROSE, F. (1955), *Tubercle*, **36**, 113.
- JEPSON, R. P., JORDAN, A., and LEVELL, M. J. (1956), *Brit. J. Surg.*, **43**, 390.
- KERN, R. A. (1957), *Amer. J. med. Sci.*, **233**, 430.
- KINSELL, L. W., PARTRIDGE, J. W., BOLING, L., and MARGEN, S. (1952), *Ann. intern. Med.*, **37**, 921.
- KIRSNER, J. B., and PALMER, W. L. (1951), *J. Amer. med. Ass.*, **147**, 541.
- KYLE, L. H., WALSH, W. P., and DOOLAN, P. D. (1953), *Arch. intern. Med.*, **91**, 283.
- LARAGH, J. H., and ALMY, T. P. (1948), *Proc. Soc. exp. Biol. (N.Y.)*, **69**, 499.
- LARKIN, M. A., and FLANNERY, M. G. (1953), *Arch. Surg. (Chicago)*, **66**, 386.
- LEVIN, M. H., RIVO, J. B., SCOTT, W., FIGUEROA, W. G., FRED, L., and BARNETT, T. F. (1953), *Amer. J. Med.*, **14**, 265.
- LEWIS, L., ROBINSON, R. F., YEO, J., HACKER, L. A., and EISEN, G. (1953), *Ann. intern. Med.*, **39**, 116.
- MCGRAW, A. B., MARGULIS, R. R., and BRUSH, B. E. (1952), *Arch. Surg. (Chicago)*, **65**, 81.
- McINTOSH, H. W., and HOLMES, C. B. (1951), *Lancet*, **ii**, 1061.
- MARGULIS, R. R., and SMITH, R. W. (1950), *J. lab. clin. Med.*, **36**, 1008.
- MONCRIEF, J. A., WEICHELBAUM, T. E., and ELMAN, R. (1954), *Surgical Forum—Proc. 39th Clin. Congr. Amer. Coll. Surg. Chicago*, October 1953, W. B. Saunders Co., Philadelphia, London, **4**, 469.
- MONTO, R. W., BRENNAN, M. J., MARGULIS, R. R., and SMITH, R. W. (1950), *J. lab. clin. Med.*, **36**, 1008.
- MOORE, F. D., STEENBURG, R. W., BALL, M. R., WILSON, G. M., and MYRDEN, J. A. (1955), *Ann. Surg.*, **141**, 145.
- NABARRO, J. D. N., STEWART, J. S., and WALKER, G. (1955), *Lancet*, **ii**, 993.
- NICHOLAS, J. A., BURSTEIN, C. L., UMBERGER, C. J., and WILSON, P. D. (1955), *Arch. Surg. (Chicago)*, **71**, 737.
- PAGE, J. A. (1954), *Brit. med. J.*, **ii**, 1334.
- PEARSON, O. H., ELIEL, L. P., RAWSON, R. W., DOBRINER, K., and RHOADS, C. P. (1949), *Cancer*, **2**, 943.
- PLOTZ, C. M., BLUNT, J. W., and RAGAN, C. (1950), *Arch. Derm. Syph. (Chicago)*, **61**, 913.
- RAGAN, C. (1953), *Bull. N.Y. Acad. Med.*, **29**, 353.
- RAGAN, C., GROKOST, A. W., and BOOTS, R. H. (1949), *Amer. J. Med.*, **7**, 741.
- RAGAN, C., LATTES, R., BLUNT, J. W., DE GUISE, V., JESSAR, R. A., and EPSTEIN, W. (1953), 'The Effect of ACTH and Cortisone upon Infection and Resistance,' Symposium on Sect. Microbiol., N.Y. Acad. Med. No. 6, March 1952, ed. Shwartzman, G., N.Y., Columbia Univ. Press, **ch. 5**.
- ROCHE, M., HILLS, A. G., and THORN, G. W. (1950), *Proc. 1st clin. ACTH Conf.*, ed. J. R. Mote, **p. 55**.
- RUSSEK, A. S. (1954), *Amer. Heart J.*, **47**, 653.
- SALASSA, R. M., BENNETT, W. A., KEATING, R. F., and SPRAGUE, R. G. (1953), *J. Amer. med. Ass.*, **152**, 1509.
- SANDBERG, A. A., EIK-NES, K., SAMUELS, L. T., and TYLER, F. H. (1954), *J. clin. Invest.*, **33**, 1509.
- SELYE, H. (1936), *Brit. J. exp. Path.*, **17**, 234.
- SELYE, H. (1946), *J. clin. Endocr.*, **6**, 117.
- SHAPER, A. G., DYSON, H. (1955), *Lancet*, **i**, 887.
- SLANAY, G., and BROOKE, B. N. (1957), *Ibid.*, **i**, 1167.
- SLAUNWHITE, W. R., and SANDBERG, A. A. (1957), *J. clin. Endocr.*, **17**, 395.
- SLOCUMB, C. H., POLLEY, H. F., WARD, L. E., and HENCH, P. S. (1957), *Ann. intern. Med.*, **46**, 86.
- SMITH, R. W., MARGULIS, R. R., BRENNAN, M. J., and MONTO, R. W. (1950), *Science*, **112**, 295.
- SMYTH, G. A. (1951), *J. Amer. med. Ass.*, **145**, 474.
- SPENCE, A. W., JENKINS, J. S., and ROBINSON, A. M. (1956), *Brit. med. J.*, **ii**, 1348.
- SPRAGUE, R. G. (1951), *Amer. J. Med.*, **10**, 567.
- SPRAGUE, R. G., POWER, M. H., and MASON, H. L. (1950), *J. Amer. med. Ass.*, **144**, 1341.
- STEENBURG, R. W., LENNIHAN, R., and MOORE, F. D. (1956), *Ann. Surg.*, **143**, 180.
- SWINTON, N. W. (1956), *Proc. roy. Soc. Med.*, **49**, 945.
- TAYLOR, A. B., ALBERT, A., and SPRAGUE, R. G. (1949), *Endocrinology*, **45**, 335.
- TEXTER, E. C., LEGERTON, C. W., RUFFIN, J. M., BOYD, J. A., and SMITH, A. G. (1953), *Arch. intern. Med.*, **91**, 744.
- THORN, G. W. (1951), 'The Diagnosis and Treatment of Adrenal Insufficiency,' 2nd edition, Charles C. Thomas, Springfield, Illinois.
- THORN, G. W., JENKINS, D., LAIDLAW, J. C., GOETZ, F. C., DINGMAN, J. F., ARONS, W. L., STREETEN, D. M. P., and MCCracken, B. (1953), *New Engl. J. Med.*, **248**, 284, 323, 369, 588, 632.
- TOMPSETT, S. L., and SMITH, D. C. (1954), *J. clin. Endocr.*, **14**, 922.
- TROEN, P., and RYNEARSON, E. H. (1955), *Ibid.*, **15**, 857.
- TRUELOVE, S. C., and WITTS, L. J. (1955), *Brit. med. J.*, **ii**, 1041.
- TULIN, M., and ALMY, T. P. (1952), *J. Amer. med. Ass.*, **150**, 559.
- TYLER, F. H., SANDBERG, A. A., and EIK-NES, K. (1953), *J. clin. Invest.*, **32**, 608.
- TYLER, F. H., SCHMIDT, C. D., EIK-NES, K., BROWN, H., and SAMUELS, L. T. (1945), *Ibid.*, **33**, 1517.
- VENNING, E. H., HOFFMAN, M. M., and BROWNE, J. S. L. (1944), *Endocrinology*, **35**, 49.
- VIDEBACK, A. A., ASBOC-MAUSEN, G., ASTRUP, P., FABER, V., HAMBURGER, C., SCHMITH, K., SPRÄCHLER, M., and BROCHNER-MORTENSEN, K. (1950), *Acta endocr. (Kbh.)*, **4**, 245.
- VIRTUE, R. W., HELMRICH, M. L., and GAINZA, E. (1957), *Surgery*, **41**, 549.
- WARD, L. E., POLLEY, H. F., SLOCUMB, C. H., and HENCH, P. S. (1953), *J. Amer. med. Ass.*, **152**, 119.
- WHITNEY, J. E., and BENNETT, L. L. (1952), *Endocrinology*, **50**, 567.

NOTICE OF SPECIAL INTEREST TO SUBSCRIBERS:

'WHY NOT HAVE YOUR COPIES OF THIS JOURNAL BOUND INTO YEARLY VOLUMES?'

You can have your twelve monthly issues fully bound in dark green pin head cloth, lettered in gilt on spine with name of journal, Volume Number and year, complete with index at front, for 21s. Od. post free. A limited number of out of print journals are available to bind into volumes and make your library complete. Price on application giving details of issues required to complete back volumes.

THE FELLOWSHIP OF POSTGRADUATE MEDICINE
60 PORTLAND PLACE, LONDON, W.1

**WHY NOT
HAVE YOUR
JOURNALS
BOUND?**