

## SURGICAL COLLAPSE DURING AND AFTER CORTICOSTEROID THERAPY\*

BY

R. I. S. BAYLISS, M.D., F.R.C.P.  
Westminster Hospital, London

Six years ago a man of 34 with rheumatoid arthritis, treated for the previous 18 months with cortisone, had a cup arthroplasty performed on his hip. He developed irreversible shock and died.<sup>1</sup> His death was due to adrenocortical failure consequent on adrenal suppression induced by the exogenously administered corticosteroid. Although attention was drawn at this time to the risks incurred whenever surgery is undertaken during the course of cortisone therapy,<sup>2</sup> there have subsequently been other instances of severe shock developing not only in patients having corticosteroid treatment at the time of surgery but also in those who had stopped treatment weeks or months before.<sup>3-12</sup>

As large numbers of patients have been, or are now being, treated with corticosteroids and may in the future require surgery for their original or some intercurrent condition, it is essential that effective measures to prevent collapse from adrenal failure are widely known, and that, should collapse develop, appropriate treatment is immediately available.

### Physiological Considerations

#### Mechanism of Adrenal Suppression

In both animals and man prolonged administration of adrenocortical hormones reduces the weight of the adrenal glands and may cause adrenal atrophy.<sup>4,13,14</sup> The decrease in anatomical mass is accompanied by loss of physiological sensitivity to pituitary corticotrophin (A.C.T.H.), which can be readily shown by a diminished output of adrenocortical hormones, as compared with a normal gland, after a standard stimulating dose of corticotrophin. This adrenal suppression is due to the exogenously administered corticosteroid inhibiting the release of corticotrophin by the hypophysis, and is in keeping with the concept that the circulating blood level of adrenocortical hormones regulates the rate of corticotrophin release from the pituitary.<sup>14,15</sup>

There is also evidence that prolonged administration of corticotrophin may also inhibit the release of corticotrophin by the patient's pituitary and interfere with the normal responsiveness of the pituitary-adrenal system to a variety of stresses, including surgical trauma.<sup>6,9</sup> Thus injections of corticotrophin induce histological changes in the pituitary similar to those found after prolonged administration of corticosteroids,<sup>16</sup> and collapse has occurred during surgery in patients who have had prolonged treatment with corticotrophin.<sup>9</sup>

#### Steroids Causing Adrenal Suppression

All the synthetic analogues of hydrocortisone currently available cause pituitary inhibition. On a weight-for-weight basis some have a greater inhibitory action than others, but since the more potent ones, such as prednisone and prednisolone, are usually given in a smaller dosage than the less potent cortisone and hydrocortisone, the resultant degree of pituitary suppression is the same.

#### Extent of Adrenal Suppression

Adrenal weight reduction and histological changes are only a rough guide to the degree of suppression, which can be assessed more accurately by studying the response of the cortex to stimulation with a standard dose of corticotrophin and measuring the output of adrenocortical hormones.<sup>17,18</sup> Investigations by Jailer and his colleagues<sup>19</sup>

suggest that the degree of adrenal suppression may be more related to the duration of corticosteroid treatment than to the dosage. Thus in one patient 100 mg. of cortisone daily for a week induced no detectable adrenal suppression, whereas, in another, 25 mg. daily for ten months produced marked unresponsiveness to corticotrophin stimulation. There are, however, wide individual variations, and, although the cause for this is unknown, it explains why some patients previously treated with steroids react badly to surgery while others do not.

#### Duration of Adrenal Suppression after Steroid Therapy

In man there are few data on how long adrenal suppression persists after stopping treatment with corticosteroids, and such as there are indicate wide individual variation. Some patients may respond normally to corticotrophin within four days of stopping treatment, whereas Christy *et al.*<sup>19</sup> found in a child of 11, who had had 75 mg. cortisone daily for a year, that 20 units of corticotrophin gel a day for 20 days failed to restore normal adrenal responsiveness.

Clinical experience also shows that there may be a very long delay before normal responsiveness returns. Patients who have stopped steroid treatment for as long as 4½ to 24 months may develop irreversible shock after even minor surgical procedures,<sup>4,40</sup> and this led the Mayo Clinic group to advocate special pre-operative preparation for any patient who had had steroid treatment.<sup>4</sup>

#### Prevention of Adrenal Suppression

Attempts have been made to prevent adrenal suppression during corticosteroid treatment by giving concurrent injections of corticotrophin, but 100 units of high-potency, long-acting corticotrophin gel weekly failed to maintain normal adrenal responsiveness, and 200-300 units weekly were not always effective.<sup>20</sup> Other workers have attempted to restore adrenal activity by giving corticotrophin pre-operatively. This too has not proved a reliable preventive of surgical collapse even when there has been apparent adrenal reactivation as judged by a normal fall in eosinophils.<sup>9</sup> As mentioned above, exogenous corticotrophin may interfere with the pituitary-adrenal response to stress, and adrenocortical failure has been reported following withdrawal of prolonged corticotrophin therapy.<sup>21</sup>

#### Clinical Considerations

Increased adrenocortical activity appears to be a normal physiological accompaniment of surgical operations.<sup>22,24</sup> In patients with Addison's disease and in those whose adrenals have been suppressed by corticosteroid treatment, minor trauma may precipitate an acute adrenal crisis despite sufficient adrenocortical function remaining to allow a life virtually free of symptoms under more ordinary circumstances. Hence any patient currently having steroid treatment and any who have had prolonged treatment during the previous 12-18 months run a risk of developing acute adrenal insufficiency during or after a surgical operation. These two types of patients constitute an absolute indication for special pre- and post-operative care. Even patients whose steroid treatment ended more than 12-18 months previously probably face an additional operative risk, but usually special pre-operative preparation is unnecessary, provided appropriate action is taken immediately if collapse occurs.

The more severe the operation the greater is the risk, but minor procedures, such as manipulation of a knee or grafting an anal ulcer, may precipitate adrenal insufficiency,<sup>6,12</sup> and special precautions must be taken no matter how trivial the undertaking. Individual variation in the degree of adrenal suppression following steroid treatment is wide, and because 7 out of 36 operations on such patients were performed uneventfully without special preparation is no reason for relaxing this precaution.<sup>25</sup>

#### Assessment of Adrenal Responsiveness Pre-operatively

The question arises whether useful practical information can be obtained by assessing pre-operatively adrenal responsiveness in patients who have had corticosteroid treat-

\*A lecture given at the Faculty of Anaesthetists, Royal College of Surgeons, on June 14, 1958.

ment in the past. The simplest technique is to study the fall in eosinophils following the injection of corticotrophin. More reliable is the increase in urinary or plasma 17-hydroxycorticosteroids after an infusion of corticotrophin or the injection of corticotrophin gel. Although such observations are of considerable interest, they are time-consuming, and impracticable in the case of an emergency operation. The results may even be misleading. Hayes and Kushlan<sup>9</sup> report a patient who had had cortisone for eight months and was prepared for operation with injections of corticotrophin. Judging by the fall in eosinophils the adrenal glands responded normally to corticotrophin stimulation, yet after being anaesthetized the patient became shocked before the incision was made. It is safer to assume the presence of adrenocortical hypofunction and take preventive measures.

### Prevention of Adrenal Insufficiency

The first essential preventive step is to know which patients coming to surgery have had or are having corticosteroid therapy, and in every instance this should be a matter for routine inquiry by the house-surgeon. The second is to dispel the still widespread belief that the administration of corticosteroids significantly impairs wound-healing and seriously lowers resistance to infection. It is this belief which has led to steroid treatment being stopped before operation and to fatal post-operative collapse.<sup>10,12</sup> There is, however, good evidence that in appropriate dosage corticosteroids do not significantly interfere with healing or increase the liability to infection.<sup>25</sup> These largely theoretical disadvantages must be weighed against the dangers of adrenocortical insufficiency, and if a hypoadrenal crisis is to be avoided more and not less corticosteroid must be given.

For patients concurrently receiving steroid treatment and for those who have had treatment during the preceding 12-18 months, the amount of additional steroid required will depend upon the severity of the operation and the degree of adrenal suppression. As both factors are difficult to assess, and too small a dose may lead to disaster, larger rather than lesser amounts should be given.

Twenty-four hours and again four hours pre-operatively the patient is given 100-200 mg. of cortisone acetate intramuscularly; and, if currently taking corticosteroids, the patient continues with his usual dose in addition. At the completion of the operation another 100-150 mg. of cortisone acetate is given intramuscularly. Subsequent treatment will depend upon whether the patient is vomiting or not. If possible 50 mg. of cortisone is given by mouth three or four times on the first post-operative day. The dosage is thereafter gradually reduced stepwise over the next week, and stopped altogether after 10-14 days in those not having current steroid treatment, or reduced to the usual maintenance dose in those who are. If the patient is vomiting, intramuscular cortisone acetate will have to be given—100-150 mg. on the first and second post-operative days and 75-100 mg. on the third. Thereafter it is usually possible to revert to oral administration. Throughout the operative period a careful check must be kept on the pulse rate and blood pressure. The development of hypotension or collapse is an indication for increased steroid treatment (see below), and it should be remembered that pyrexia may be a sign of adrenal insufficiency.

This regimen is based on the evidence that a severe stress causes the adrenal glands to secrete the equivalent of 400 mg. of hydrocortisone daily, and that intramuscular cortisone acetate is slowly absorbed—not producing any detectable increase in the plasma steroid level for 6-10 hours, and providing a depot which lasts for several days.

### Treatment of Adrenocortical Collapse

For patients who have stopped steroid treatment more than 12-18 months before, it is usually safe to omit pre-operative cortisone coverage provided the treatment out-

lined below is immediately available if collapse develops during or after the operation. The same measures should be taken if shock occurs in patients already having additional supportive steroid therapy. Provided hypotension is detected early and action taken at once, the patient will respond promptly.<sup>9,12</sup> Because of its slow rate of absorption, intramuscular cortisone or hydrocortisone has no place in the immediate treatment of collapse, nor, because of the uncertainty of the adrenal response, is corticotrophin of value.

The keystone of treatment is intravenous hydrocortisone given as the water-soluble hemisuccinate, 134 mg. of this salt containing 100 mg. hydrocortisone. Here, too, it is wiser to be over-generous in the amount given. As soon as collapse occurs 100 mg. of hydrocortisone is given over two hours by intravenous drip in 500 ml. of 5% glucose. During the first 24 hours 400 mg. of hydrocortisone may have to be infused in 1-1½ litres of fluid. If the hypotension is not corrected quickly, 2-4 mg. of noradrenaline is added to the infusion bottle.

### Summary

Corticosteroid therapy, especially if prolonged, causes adrenal suppression. Surgical procedures increase the need for adrenocortical secretions, and may lead to fatal collapse in patients who are currently receiving steroid therapy or who have had such treatment within the previous two years.

To prevent disasters it is essential to know before operation whether the patient is having or has had steroid therapy. Patients currently having steroid treatment need more, not less, corticosteroid during the operative period. They and those who have had steroid treatment during the previous 18 months should be given 100 to 200 mg. of cortisone acetate intramuscularly 24 hours and again 4 hours pre-operatively. Post-operatively 100 to 200 mg. of cortisone is given daily and gradually reduced over a period of a week—by mouth if the patient is not vomiting, by intramuscular injection if he is.

It is usually safe to omit special pre-operative measures in patients who have stopped steroid therapy more than 18 months previously, provided a careful watch is kept on the pulse and blood pressure and, if collapse occurs, immediate treatment is available with intravenous hydrocortisone hemisuccinate in a dose of 100 to 400 mg. per 24 hours.

### REFERENCES

- Fraser, C. G., Preuss, F. S., and Bigford, W. D. (1952). *J. Amer. med. Ass.*, **149**, 1542.
- J. Amer. med. Ass.*, 1952, **148**, 1422.
- Lewis, L., Robinson, R. F., Yee, J., Hacker, L. A., and Eisen, G. (1953). *Ann Intern. Med.*, **39**, 116.
- Salassa, R. M., Bennett, W. A., Keating, F. R., and Sprague, R. G. (1953). *J. Amer. med. Ass.*, **152**, 1509.
- Harnagel, E. E., and Kramer, W. G. (1955). *Ibid.*, **158**, 1518.
- Downs, J. W., and Cooper, W. G. (1955). *Amer. Surg.*, **21**, 141.
- Kitredge, W. E. (1955). *J. Urol.*, **73**, 585.
- Hayes, M. A. (1956). *Surgery*, **40**, 945.
- and Kushlan, S. D. (1956). *Gastroenterology*, **30**, 75.
- Allanby, K. D. (1957). *Lancet*, **1**, 1104.
- Plumer, J. N., and Armstrong, R. S. (1957). *Arizona Med.*, **14**, 202.
- Slaney, G., and Brooke, B. N. (1957). *Lancet*, **1**, 1167.
- Ingle, D. J. (1938). *Amer. J. Physiol.*, **124**, 369.
- Sayers, G., and Sayers, M. A. (1949). *Ann. N.Y. Acad. Sci.*, **50**, 522.
- (1950). *Physiol. Rev.*, **30**, 241.
- Bennett, W. A. (1954). *J. Bone Jt Surg.*, **36A**, 867.
- Bayliss, R. I. S., and Steinbeck, A. W. (1954). *Brit. med. J.*, **1**, 486.
- Cope, C. L., and Black, E. (1958). *Ibid.*, **1**, 1020.
- Christy, N. P., Wallace, E. Z., and Jailer, J. W. (1956). *J. clin. Endocrinol.*, **16**, 1059.
- Young, I. I., de Filippis, V., Meyer, F. L., and Wolfson, W. Q. (1957). *Arch. intern. Med.*, **100**, 1.
- Richman, A., Sternlieb, I., and Winkelstein, A. (1956). *Amer. J. digest. Dis.*, **1**, n.s., 206.
- Bayliss, R. I. S. (1955). *Brit. med. J.*, **1**, 495.
- Franksson, C., and Gemzell, C. A. (1955). *J. clin. Endocr.*, **15**, 1069.
- and von Euler, U. S. (1954). *Ibid.*, **14**, 608.
- Poptert, A. J., and Davis, P. S. (1958). *Lancet*, **1**, 21.