

Present Status of the Problem of Iatrogenic Adrenal Cortical Insufficiency

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ALTHOUGH adrenal insufficiency may be produced by many conditions which cause destruction of the adrenal gland or anterior pituitary gland, the most common cause of adrenal cortical insufficiency is that which is produced by the practitioner himself.¹ This type of adrenal insufficiency has resulted from the administration of corticosteroids in varying amounts to large numbers of patients for the treatment of many nonendocrine conditions. The acute mechanism by which this comes about is simple. Therapeutic doses of corticosteroids usually inhibit ACTH secretion by the pituitary gland. The adrenal cortex atrophies in the absence of ACTH and becomes relatively unresponsive to ACTH. Patients with atrophic adrenal glands subjected to a stressful situation, such as surgical trauma, may develop acute adrenal insufficiency and succumb to the lack of adrenal hormone. Subjects receiving corticosteroids therapeutically usually require an increased quantity of adrenal steroid when subjected to increased stress. This acute type of adrenal insufficiency, occurring in patients receiving corticosteroids, is more easily recognizable, however, than that which has been observed in patients who have discontinued therapy but who still have an atrophic adrenal cortex which does not respond to stress. The following discussion will be directed particularly toward this group of patients, and an attempt will be made to explain the mechanism by which prolonged adrenal cortical insufficiency, which may be present months or years following discontinuance of corticoid treatment, is produced.

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Diagnosis of Adrenal Insufficiency

The three common types of adrenal insufficiency are likely to present in very different ways. The diagnosis of typical primary adrenal insufficiency or Addison's disease is not difficult. The classical findings of increased skin pigmentation, hypotension, hyponatremia, and hyperkalemia with elevated blood urea nitrogen, present a picture which is readily recognizable. The patient with so-called secondary adrenal insufficiency resulting from panhypopituitarism and lack of ACTH secretion is less easily recognized. These patients do not have the pigmentation or other plasma chemical changes which are commonly associated with Addison's disease. The continued secretion of aldosterone in patients with pituitary insufficiency maintains electrolyte balance in an essentially normal state, at least in the unstressed patient. The patient with panhypopituitarism is often recognized by loss of body hair, decreased libido, amenorrhea in the female, less commonly by the signs and symptoms of hypothyroidism which rarely accompany the disease, or finally by shock occurring following stress. Iatrogenic adrenal cortical insufficiency fails to produce any of the physical stigmata of adrenal insufficiency referred to above, which are associated with Addison's disease or panhypopituitarism. Adrenal cortical therapy does not suppress aldosterone production or the mechanisms for its maintenance, thus serum electrolytes are normal. The pituitary gland continues to secrete normal quantities of pituitary hormones other than ACTH with resultant normal function of other endocrine glands which are under pituitary control.

The estimation of urinary adrenal cortical

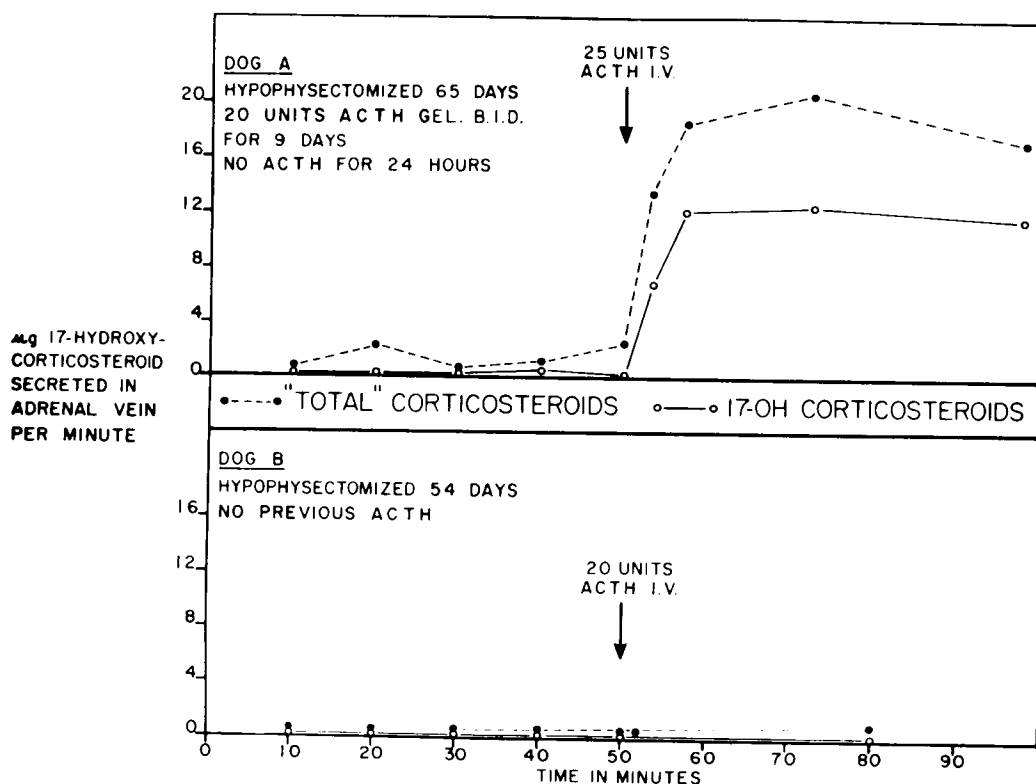


FIG. 1. Response to ACTH of two hypophysectomized dogs as demonstrated by measurement of corticosteroids secreted into the adrenal vein. Dog A was given ACTH to produce adrenal hypertrophy prior to the study whereas dog B had received no previous ACTH.

hormones following ACTH administration is the definitive test in making a diagnosis of adrenal insufficiency. The most widely-used procedure consists of intravenous administration of ACTH (we currently prefer 50 units in saline) over 8 hours on two successive days with collection of 24-hour urine samples for estimation of 17-hydroxy- or 17-ketocorticosteroids. Failure of the output from the adrenal gland to increase following ACTH, as reflected by the measurement of urinary corticoids, is good evidence of adrenal destruction and probably the best evidence of the presence of Addison's disease. The patient with hypopituitarism or an atrophic adrenal resulting from previous corticoid therapy will, under these circumstances, fail to demonstrate an increased cortical output on the first day of administration, but then will have a progressively increasing cortical output on suc-

cessive days. Thus it has been found necessary to administer ACTH for three to four days in such subjects, to demonstrate that the difficulty is clearly not adrenal cortical destruction but rather secondary adrenal cortical atrophy. It should be emphasized that estimation of baseline urinary corticoids in such subjects without ACTH administration is of little value in making this diagnosis. The difference between normal and low values of adrenal cortical hormones, as commonly measured in the urine, is a small one. Many patients with proven primary adrenal insufficiency will, on determination of urinary corticoids without ACTH administration, be found to have normal levels of adrenal hormones. It is necessary, therefore, in order to make an objective diagnosis of iatrogenic adrenal cortical insufficiency, as well as the diagnosis of other types of adrenal insufficiency, to estimate the func-

tional reserve of the adrenal gland. This is done by the administration of intravenous ACTH as indicated above.

Initial diagnosis of iatrogenic adrenal cortical insufficiency is usually made first, by knowledge that the patient has received corticosteroid therapy, and second, by the signs and symptoms of adrenal cortical insufficiency which may occur following stress. Although many patients, during the early period following cessation of corticosteroids, may complain of malaise or tiredness,² they are unlikely, as noted above, to have specific physical findings or symptomatology suggestive of adrenal insufficiency. Following trauma, surgery, or acute infection, there is an increased corticoid requirement which cannot be supplied by the atrophic gland; the patient may, therefore, develop a picture of adrenal cortical insufficiency and shock as the first evidence of insufficiency, if a careful history of previous medication has not been obtained.

Mechanism of Production of Adrenal Atrophy Following Corticosteroids

Within a few hours following hypophysectomy or administration of corticosteroids in doses large enough to suppress secretion of ACTH by the pituitary gland, there is almost complete cessation of corticosteroid secretion.³ This is accompanied by marked atrophy of the adrenal cortex and relative unresponsivity of the gland develops. This is illustrated in figure 1. In this case, two dogs were hypophysectomized approximately two months previously. Following this, dog A was given ACTH for a period of nine days but none for the 24 hours prior to carrying out the experiment. Each dog was then operated upon to insert a cannula into the adrenal vein; in neither case was there a significant increase in corticosteroids during the first 40 minutes as would have occurred in a normal animal. In dog A, however, the gland was of approximately normal size as the result of nine days of ACTH administration immediately preceding adrenal cannulation; and there was a good corticoid response when a large dose of ACTH was administered intravenously. On the other hand, when a large dose of ACTH was given intravenously to dog B, it had no immediate effect on corticosteroid secretion. This was due to

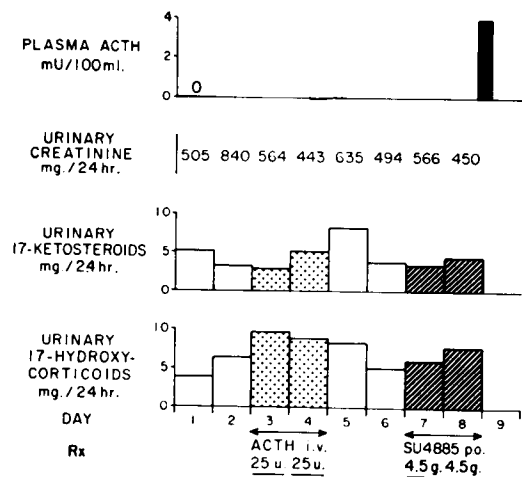


FIG. 2. Study of a patient who had adrenal atrophy following discontinuance of corticosteroid therapy. Although the adrenal failed to respond to administered ACTH, there was a marked increase in plasma ACTH when methopyrapone (Metopirone, SU-4885) was given.

the atrophy of the adrenal gland which had not been stimulated by ACTH over a long period of time and could not, therefore, respond acutely to such stimulation. This situation is similar to that in the patient who has been receiving corticosteroids, in which case there will be atrophy of the adrenal and no response to ACTH.

It has been suggested that the relative lack of responsiveness of the adrenal cortex following corticoid therapy must be due to inability of the pituitary gland to secrete ACTH.³ Studies, however, have demonstrated that when appropriately stimulated the pituitary gland may, in some of these patients, produce very large quantities of ACTH.⁴ This is illustrated in figure 2. This patient who had received prednisone, 15 mg. daily for two years, and then had received no corticosteroid for approximately three months prior to these studies, had done very well during the interim period. Urinary 17-hydroxy- and 17-ketosteroids were normal but failed to increase significantly during two days' stimulation by ACTH. On treatment with the substance methopyrapone^o (Metopirone, SU-4885), there was failure of the adrenal cortical ster-

^o Methopyrapone has been shown to block the enzymatic synthesis of hydrocortisone.

oids to increase in the urine, but there was a significant increase in plasma ACTH. Similar findings were demonstrated for six of 16 such patients studied. This would indicate that in these subjects the pituitary gland was capable of producing ACTH, but that the adrenal gland was unresponsive. Other studies have demonstrated that the responsivity of the adrenal gland can be restored for a short period of time at least by continued administration of ACTH.⁵ It would appear, therefore, that there is adrenal atrophy due to lack of ACTH production, which does not represent a loss of ability to produce ACTH but rather a relative failure of those mechanisms which bring about ACTH secretion in the normal subject. Such a relative loss in sensitivity of ACTH control mechanisms presumably has occurred as the result of continued administration of high doses of exogenous corticosteroids.

Treatment of Iatrogenic Adrenal Insufficiency

It has been suggested that there may be value in gradual reduction of the corticosteroid, administration of ACTH throughout the period of corticosteroid therapy, or ACTH treatment, as a concluding mode of therapy to bring about restoration of the gland to normal size.² There is no doubt that administration of ACTH, either with the corticosteroids or as a concluding part of hormonal therapy, will act to maintain adrenal size and, therefore, assure immediate responsivity to ACTH administration or its endogenous production. This is, however, the acute situation. Evidence has been presented that patients treated with ACTH and no corticosteroids are likely to have the same chronic problem as those treated with corticosteroids alone.⁶ If the postulated mechanism above is correct, this seems likely. The problem is not one of damage to the adrenal or to the pituitary gland but the effect of high levels of corticosteroids on central nervous system centers which control ACTH secretion. Thus high levels of corticosteroids maintained over a long period of time by corticosteroid or by ACTH administration appear to have similar effects and result in blunting of normal ACTH control mechanisms. One would have to conclude on this basis that ACTH therapy has little value in patients who

are receiving or have received corticosteroids.

The treatment of acute adrenal insufficiency, irrespective of etiology, is fairly well standardized. This consists of administration of large quantities of corticosteroids, of antibiotics if infection is present, and whatever other means may be necessary for the proper therapy of the shock that may occur. The most essential part of this therapy is the corticosteroid given intravenously and in large quantities. Our own preference is to give at least 100 mg. of cortisol every 8 hours for the first 24 hours of a stressful procedure, and then to decrease the dose by 50 per cent a day if the patient has responded and is doing well; decrease is less rapid if the clinical course is complicated by a stressful situation.

It should be remembered that only a relatively small percentage of patients who have been treated with corticosteroids, are likely to have developed this defect. It has been our policy to have corticosteroids available for immediate intravenous administration in the patient in whom adrenal insufficiency is suspected, but not to routinely administer corticosteroids unless the patient has received therapy during the last few months. Paris *et al.*³ suggest that corticosteroids should be given preoperatively and during surgery to all patients who have shown signs of hypercortisolemia within 9 months of the procedure. Early treatment is important in the prevention of irreversible shock; when in doubt, corticosteroids should be administered. More complete diagnostic procedures may be carried out at a later date if thought necessary. Although with most drugs, the possibility of complications ends with discontinuance of administration of that drug, in the instance of the corticosteroids a defect in adrenal response may persist for some years following therapy. Thus, patients have been described who at post-mortem examination had adrenal atrophy three years following discontinuance of corticosteroid therapy.

Summary

The diagnosis, mechanism of production and therapy of adrenal cortical insufficiency resulting from corticosteroid therapy have been discussed. The diagnosis of this condition is usually made following development of signs

and symptoms of adrenal insufficiency following stress. Although ACTH infusion with estimation of urinary corticoids will demonstrate the deficiency, routine urinary corticoids are likely to be normal. Present evidence suggests that the primary defect in these patients is a failure in normal ACTH control mechanisms, but not a primary defect in adrenal or pituitary. Therapy should be dictated by constant awareness of the problem in patients who have previously received corticosteroids, and the immediate administration of intravenous corticosteroids to any patient who shows any sign of adrenal insufficiency during stress.

References

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PULMONARY EMBOLISM Circulatory and ventilatory effects of pulmonary embolization with radioactive-labeled barium sulfate emulsion were measured in thiopental-anesthetized sheep. Within 10 to 12 seconds after injection of the emulsion there was a sharp rise in pulmonary artery pressure, pulmonary arterial resistance, percentage venous admixture, respiratory rate and total ventilation, with a drop in cardiac output, systemic arterial pressure, arterial oxygen saturation and lung compliance. Repeated injections of material led to increasingly severe symptoms. Isoproterenol by vein or aerosol was remarkably effective in reversing these events when used either prophylactically or curatively. During its continuous infusion, sheep tolerated 6 to 7 serial injections of embolic emulsion before death. When animals with postembolic collapse were given isoproterenol intravenously, they promptly resumed breathing, pulmonary and systemic arterial pressures rose and 9 of 11 such sheep recovered. Although there was some evidence of slight efficacy of epinephrine used similarly, both norepinephrine and hypertensin were completely ineffective. The usefulness of isoproterenol in the emergency treatment of pulmonary embolization in man is predicted. (*Halmagyi, D. F. J., and others: Effect of Isoproterenol in Experimental Lung Embolism With and Without Postembolic Collapse, Amer. Heart J.* **65**: 208 (Feb.) 1963.)

NEUROMYOPATHY The neurologic symptomatology of either metastatic or non-metastatic neoplasms may be divided into three groups: (1) carcinomatous encephalomyeloneuropathy, (2) progressive multifocal leucoencephalopathy, and (3) the myopathic-myasthenic syndrome. In the latter group the onset of the muscular symptoms is usually insidious but has sometimes been precipitated by the administration of a muscle relaxant in connection with anesthesia for operation. This produces severe weakness, indicating a disorder of muscle function involving the myoneural junction. (*Brain, W. R.: The Neurological Complications of Neoplasms, Lancet* **1**: 179 (Jan. 26) 1963.)