

## CORTISONE PROBLEMS INVOLVING ANESTHESIA \*

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CORTISONE (cortone®) has been approved by the Federal Food and Drug Administration and has been accepted by the American Medical Association for use in the conditions listed in table 1.†

The use of cortisone and corticotrophin (ACTH) in rheumatoid arthritis, some types of allergy, rheumatic fever and several other diseases may create an endocrine disturbance in many of the patients (1). One aspect of endocrine disturbance resulting from the use of these agents is depression of adrenal cortical function. Hence, the anesthesiologist must familiarize himself with the use and abuse of these hormones, because it is a fact that patients can reach the operating table, particularly in emergencies and many times in elective surgical operations, without the surgical team realizing some factors that should be known in advance.

As the use of cortisone and corticotrophin (ACTH) becomes more widespread, as a result of better preparations, lower cost and a better understanding of how to employ them, the anesthesiologist will find that he will encounter patients who previously have been treated with cortisone. If, during anesthesia and operation on one of these patients, unexplained shock develops and if the response to the usual treatment is unsatisfactory, the anesthesiologist must be ever alert to the possibility that the patient may have an unrecognized depressed adrenal cortical function for some reason. In such an emergency he must resort to treatment aimed at amelioration of depressed adrenal cortical function.

The circumstances I have just sketched eventually could lead to modification of our present methods of the treatment of shock during and after operation. The basis for this conjecture is the physiologic fact that some patients may not have sufficient adrenal cortical function to maintain themselves adequately under conditions of stress, even though they may never have received cortisone or ACTH. Already there are surgeons who prepare their patients for operation by treating them as if they were deficient in adrenal cortical function.

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TABLE 1  
CONDITIONS IN WHICH CORTISONE CAN BE ADMINISTERED  
WITH APPROVAL OF:

1. American Medical Association and  
Federal Food and Drug Administration

Rheumatoid arthritis and variants, such as:

Rheumatoid spondylitis (Marie-Strümpell disease)

Still's disease

Psoriatic arthritis

Acute rheumatic fever

Disseminated lupus erythematosus

Allergic states

Allergic dermatitis

Bronchial asthma

Sensitivity to drugs

Angioneurotic edema

Diseases of the eyes

Iritis

Iridocyclitis

Chorioretinitis

Uveitis

Retinitis centralis

Herpes zoster ophthalmicus

Retrobulbar neuritis

Optic neuritis

Sympathetic ophthalmia

Choroiditis

Nonspecific superficial keratitis

Deep keratitis

Acne rosacea keratitis

Phlyctenar keratoconjunctivitis

Allergic conjunctivitis

Mild acute iritis

Chronic iritis

Diseases of the skin

Pemphigus

Atopic dermatitis

Exfoliative dermatitis, including lesions of the skin secondary to drug reactions

Addison's disease

Leukemias and lymphomas

Acute leukemia

Chronic lymphatic leukemia

Lymphosarcoma

Hodgkin's disease (transient involution of neoplasm)

2. Federal Food and Drug Administration

Allergic states

Hay fever

Serum sickness

Transfusion reaction

Diseases of the eyes

Retrolental fibroplasia

Corneal injuries—opacities

Conditions of the skin

Scleroderma

Dermatomyositis

Other conditions

Adrenogenital syndrome

Waterhouse-Friderichsen syndrome

TABLE 1—Continued

Sarcoidosis
Bursitis
Early periarteritis nodosa
Hunner's ulcer
Sprue
Adrenalectomy for hypertension, Cushing's syndrome, or neoplastic diseases
Berylliosis
Laryngeal edema
Acquired hemolytic anemia
Allergic purpura
Rh incompatibilities
Incurable disease such as carcinoma and Hodgkin's disease (to bring about sense of well-being)

One of the seemingly common characteristics of circulatory collapse among patients who at some time previous to operation have been treated with cortisone or ACTH, but who have not received it pre-operatively, during and after operation, is that circulatory collapse occurs at the time of operation or up to twenty-four to thirty-six hours after operation. Another characteristic is that the onset of the shock is sudden and extreme, and there is little or no time in which to combat it after it has begun.

It would seem eminently wise that, if it is possible to do so, such a grave condition be treated prophylactically. Patients afflicted with this type of shock can be supported temporarily by the use of solutions of "plasma volume expanders" such as dextran, polyvinylpyrrolidone and gelatin containing a small quantity of levophed <sup>®</sup>, ephedrine, or neosynephrine. These measures, however, are of temporary value. The anesthesiologist must not lose sight of the fact that cortisone is essential to life, and that it must be provided to these patients just as it must be provided to patients who have undergone bilateral extirpation of the adrenal glands.

A case illustrative of this dangerous situation has been reported by Fraser, Preuss and Bigford. The case seems to represent a fatality arising from adrenal cortical atrophy plus the stress of anesthesia and operation (2). The case they report is as follows:

"A 34-year-old man had had rheumatoid arthritis for a period of seven years. Almost every joint of his body was involved, particularly the hips, where there was a marked flexion contracture. The patient had been receiving cortisone for eight months. He first received 1,200 mg. of cortisone over a period of 10 days and then 100 mg. three times weekly. For two months prior to the present examination the patient had been taking 25 mg. of cortisone twice a day. Because of the pain in the right hip and flexion deformity, a cup arthroplasty in the right hip was advised.

"*Past History.*—The patient had the usual childhood diseases, including smallpox, and had hay fever. Several episodes of mild skin petechiae were diagnosed as allergic purpura; the latest occurred after his use of cortisone. Bleeding, clotting, and prothrombin times were normal. The platelet count was normal.

*Physical Findings.*—Physical examination revealed a chronically ill-appearing, deformed man of 34 years, who was able to walk about in a stooped position with the use of crutches. He did not appear to be in acute pain. There was pronounced evidence of generalized rheumatoid arthritis. The heart and lungs were normal.

*Laboratory Data.*—X-ray studies revealed an essentially normal chest. The heart measured nearly 50 per cent of the transverse diameter of the chest and was not enlarged in any one region. The red blood cell count was 4,220,000 and hemoglobin 13 Gm. per 100 cc. Urinalysis disclosed no abnormalities. Serologic studies revealed nothing essentially abnormal. The white cell count was 11,000 with 72 per cent neutrophils, 19 per cent lymphocytes, 8 per cent monocytes, 1 basophil, and no eosinophils.

*Course in the Hospital.*—The patient received cortisone up to the time of admission and two days later was taken to the operating room. Spinal anesthesia was employed, with tetracaine (pontocaine) hydrochloride supplemented with thiopental sodium. The blood pressure at the beginning of the operation was 140/80 and the pulse rate 72. A routine cup arthroplasty of the right hip was performed. During the course of surgery the patient received one blood transfusion. His blood pressure did not fall below 110/80 during the whole procedure. After the first unit of blood was given, the second was begun. After the patient received 50 cc. of the second transfusion some muscular twitchings were noted, so that transfusion was discontinued to guard against a transfusion reaction. During the course of the surgery the patient never showed any real need for further supportive therapy. His blood pressure never went below 110/80 and his pulse rate never higher than 80. The operation extended over a period of an hour and one-half. Almost immediately after being transferred from the operating table to the bed the patient began to show some fall in blood pressure. The first postoperative blood pressure reading was 86/60, so that transfusion of another unit of blood was begun. In spite of rapid administration of 500 cc. of blood, the blood pressure continued to decline. A total of 250 cc. of plasma was given without appreciable change. It was felt at this time that there was something peculiar about this patient's reaction, because his estimated blood loss at surgery was not over 500 cc. and he had been given more than adequate replacement, but the blood pressure continued to decline. Five cubic centimeters of adrenal cortical extract was given on two occasions without benefit, and 500 cc. of plasma was given rapidly. In spite of this therapy, the blood pressure declined to about 40 systolic and the pulse became almost imperceptible. Five minims (0.3 cc.) of epinephrine was given intravenously without effect. Epinephrine was then given intracardially without effect. Instead of showing the usual signs of vasomotor collapse and shock, the patient appeared somewhat flushed, his respirations were labored, and he appeared to have air hunger. His axillary temperature rose to 102 F. The patient lost consciousness and died three hours after surgery.

*Autopsy Findings.*—An autopsy was performed 21 hours after death. There was evidence of marked generalized rheumatoid arthritis. The operative area revealed a moderate amount of hemorrhage, which did not exceed that usually associated with this type of operation. There were multiple small parenchymatous hemorrhages in the lungs and a small subendocardial hematoma in the left ventricular aspect of the interventricular septum. All abdominal viscera were severely congested. The most striking observation was pronounced atrophy of both adrenals (see the accompanying figure).

*“Microscopic Observations.*—Microscopic examination of the tissue confirmed the gross findings. The three layers of the adrenal cortex were still identifiable, but each was markedly reduced in width. The cortical cells revealed no appreciable changes. The medulla was likewise atrophic. There were also a few petechiae in the brain parenchyma. The kidneys showed no evidence of a transfusion reaction. Negative Sudan IV stains of brain, lungs and kidneys ruled out fat embolism.”

The rôle of the adrenal and other endocrine glands in connection with anesthesia and operation was discussed recently by Patrick, Underdahl and Adams (3). They pointed out that the condition of insufficiency of the cortex of the suprarenal gland must be recognized when it occurs, and they formulated recommendations concerning patients with pheochromocytoma and those with Addison's disease and Cushing's syndrome. They discussed other endocrine glandular conditions as well.

Perhaps the most satisfactory schedule for preparing for anesthesia and operation those patients who have suppression of adrenal cortical function consists of the intramuscular administration of 100 to 200 mg. of cortisone per day for two to three days before operation and again on the day of operation (4). A similar schedule also may be used for two or three days postoperatively; after that, the dose should be gradually reduced until it reaches the previous optimal figure.

On the other hand, there are instances of emergency in which a patient requires anesthesia and immediate operation. In such cases no such schedule of treatment is possible. Hence, it is imperative to ask such a patient or someone who can speak for him whether or not he has been receiving cortisone or ACTH.

In such emergencies, about 30 to 50 cc. of adrenocortical extract injected intravenously and repeated as needed, in addition to resumption of the use of cortisone or ACTH, has been employed to maintain the unprepared patient safely during the period of stress, so that he may be assured of the support necessary for survival. Cortisone (free alcohol) is used intravenously. According to the manufacturers, it should be prepared as follows.

Suspend 100 mg. of sterile cortisone (free alcohol) in 500 cc. of saline solution and autoclave at 121 C. for thirty minutes in a suitable stoppered flask. This will dissolve the cortisone (free alcohol). This material should then be kept in an incubator or suitable constant-temperature apparatus at 37 C. until used. Ideally, the preparation should be used within twenty-four hours. However, longer periods may elapse, provided the solution is kept at 37 C. and that a cloudy precipitate has not formed. If this solution is not maintained at a temperature of 37 C. or higher, there is a tendency for the free alcohol to come out of solution and form a cloudy precipitate.

Very recently a preparation has been made available in which 100 mg. of compound F or hydrocortisone is used in 500 cc. of isotonic solution of sodium chloride. This preparation is bottled and is ready

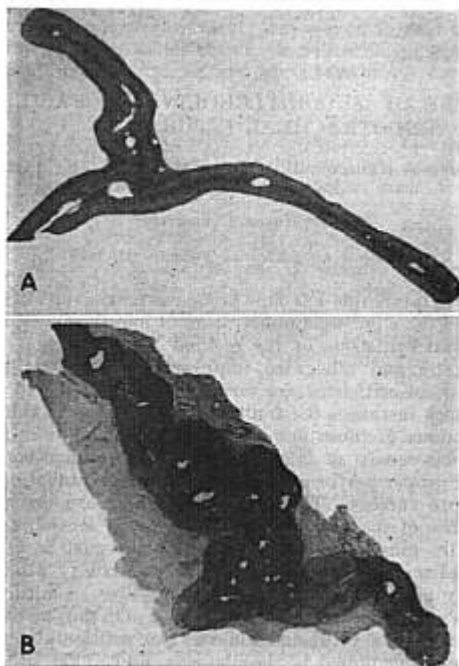


FIG. 1. *A*, cross section of the entire adrenal gland, showing marked adrenal atrophy ( $\times 10$ ). *B*, cross section of a normal adrenal gland ( $\times 10$ ). (Reproduced with permission from Fraser, C. G., Preuss, F. S. and Bigford, W. D.: Adrenal Atrophy and Irreversible Shock Associated With Cortisone Therapy, *J. A. M. A.* 149: 1542-1543 [Aug. 23] 1952.)

for use at any time, just as standard solutions for parenteral use are available.

The patient who shows evidence of hypercortisonism must be treated as is the patient who has suppression of adrenal cortical function.

#### REFERENCES

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