ABSTRACTS

This section of the ANNALS is published in collaboration with the three abstracting journals, ABSTRACTS OF WORLD MEDICINE, ABSTRACTS OF WORLD SURGERY, OBSTETRICS AND GYNAECOLOGY, and OPHTHALMIC LITERATURE, published by the British Medical Association.

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism: Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Sciatica: Gout: Non-Articular Rheumatism: General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with steroid research which, although not directly concerned with the rheumatic diseases, may make an important contribution to knowledge of the scope and modus operandi of steroid therapy.

Acute Rheumatism


The authors discuss the effects of ACTH and cortisone on rheumatic carditis and endocarditis and the lack of agreement on dosage—Coste advocating the use of a constant daily dosage (10 mg ACTH or 120 mg cortisone) for about 6 weeks, and Hench favouring larger doses for about 10 days followed by smaller ones. As the hormones are in short supply, the authors decided to use them for initial therapy only, thereafter continuing with salicylates. They consider that with this "coupled treatment", as they call it, the worst side-effects of either remedy given by itself are avoided. Cortisone is preferred to ACTH and, in adults, they give 300 to 400 mg on the first day (divided into four doses), 200 to 300 mg on the second, and 100 to 200 mg on the third (and sometimes) on the fourth; the total dosage is thus between 600 mg and 1 g cortisone. Without further treatment a relapse can be expected on the fifth day, and it is therefore important to start salicylate treatment without delay, the authors giving sodium gentisate by mouth (14 g daily in several doses) and sodium salicylate by intravenous injection (4 g daily in two doses). Details are given of eighteen patients treated, twelve of whom were in their first attack of rheumatic fever and six cases of relapse. It is claimed that this form of treatment is both efficacious and the most economical way of using the hormones in the treatment of rheumatic fever. [The original article should be consulted for clinical details.]

D. PREISKEL.

Systemic Arterial Embolism in Rheumatic Heart Disease.


The authors studied 194 patients with rheumatic heart disease diagnosed clinically or at necropsy (39 cases) during the years 1923-50. A mitral lesion was present in 188; auricular fibrillation, usually of some duration, but less often paroxysmal or of recent origin, occurred in 174 patients. There was little evidence that digitalis was a significant factor, and in only one of eleven patients treated with quinidine was embolism possibly due to restoration of normal rhythm. [Normal rhythm was not restored in the other cases.] Moderate rather than extreme left auricular enlargement was usually present. Cardiac failure, exercise, surgical operations, and pregnancy did not appear to be precipitating agents. Embolic or cardiac thrombi were present in 25 of the 39 cases. Emboli coming to necropsy, and a probable site of origin was seen in six others. The thrombus was in the cavity of the left auricle in eleven, in the auricular appendage alone in ten, and in both in four cases. Active rheumatism was present in nine cases, in eight of which there was a visible thrombus.

Emboli to the number of 393 were observed in the 194 patients, who varied in age from 7 to 74 years: 48 per cent. were to the brain, 14 per cent. to the arteries of the abdominal viscera, 11 per cent. to the aortic bifurcation, and iliac arteries, 17 per cent. to the arteries of the lower extremity, and 10 per cent. to the arteries of the upper extremity. Of the 194 patients, 71 per cent. are known to be dead: 12 per cent. from the initial embolus, 28 per cent. from subsequent emboli, and most of the remainder from cardiac failure. The highest mortality from all causes was in the first year after the initial embolus, but fatal emboli continued to occur 10 or more years later. Particularly dangerous sites were the cerebral vessels (64 deaths in 130 patients) and mesenteric arteries (ten deaths in eleven patients).

Early recognition, prompt embolectomy, and the use of anticoagulants are stressed as essential in cases with emboli to the aortic bifurcation and lower limbs. No treatment is considered to improve the prognosis of cerebral embolism. The prophylaxis of recurrent embolism is also discussed, including the continued use of anticoagulants over long periods, the avoidance of too rapid diuresis by digitalis or mersalyl, administration of quinidine, and amputation of the auricular appendage.

[This is an important paper which should be read in detail by all interested in this subject.] J. W. Litchfield.


In studying the effect of any therapeutic agent in a self-limiting disease such as rheumatic fever it is important to note the point in the course of the disease at which the agent is administered, as the effect is likely to vary considerably at different stages. For the purpose of analysis of the effects of treatment with cortisone and ACTH the
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authors’ patients were therefore classified into the following categories:
(1) those with acute rheumatic fever in the first attack and without cardiac damage (eight cases);
(2) those with acute rheumatic fever in the first attack, but complicated by rheumatic carditis (two cases);
(3) those with a recurrent attack of rheumatic fever complicated by previous cardiac damage (four cases).

The authors found that the hormones suppressed the acute manifestations of rheumatic fever, but that until the disease had run its usual course exacerbations occurred when they were discontinued. To be most effective it seemed that the hormones should be given in adequate amounts early in the acute phase of the attack and administration continued in reduced amounts until the activity of the disease is at an end. The authors state that their experience in these cases gives rise to the hope that early adequate administration of these hormones in initial or subsequent attacks of rheumatic fever may prevent or minimize permanent cardiac damage in a majority of cases, although it will need several years of follow-up before it can be seen how fully this hope is justifiable. Only in one case had treatment to be discontinued owing to the occurrence of side-effects.

W. S. C. Copeman.


Anaemia, of sudden onset and at times severe, is a well-known feature of rheumatic fever. Previous studies have revealed no evidence of increased blood destruction. In 1938 it was regarded as a fault in erythropoiesis, until Bradley brought evidence to show that the apparent anaemia is only relative, resulting from increased plasma volume.

Further evidence that the anaemia is a dilution phenomenon is recorded in this paper. Estimations of the haemoglobin, haematocrit, and number of erythrocytes were made in ten patients with rheumatic fever; fluid balance studies were made in each case. In one patient, frequent plasma volume determinations were made, and the results plotted against the corresponding haemoglobin levels. The anaemia was found to be normocytic, normochromic, or slightly hypochromic. Repeated estimations throughout the course of the disease showed a close direct relationship between haemoglobin and packed cell volume; a rise in haemoglobin was associated with increase in fluid output over intake; and a striking inverse relationship was demonstrated between haemoglobin levels and plasma volume.

An inverse relationship was also shown between haemoglobin and erythrocyte sedimentation rate, the haemoglobin level serving as a good indication of rheumatic activity. The author suggests that hydraemia and changes in the osmotic pressure of the plasma may be important factors in this and other anaemias associated with infection.

Kenneth Stone.


The author estimated QTC in 82 rheumatic children and twenty non-rheumatic controls. Taking 0.422 as the upper limit of normal, QTC was found to be prolonged in 12 per cent. of the recordings from rheumatic children and in none of those from the controls.

The rheumatic children were considered in three groups: those suffering from rheumatism with and without active carditis and those with inactive rheumatic heart disease. There was no clear difference in the frequency of prolonged QTc in these groups, so that QTc estimation is not a reliable guide to the diagnosis of active carditis. In an occasional case however, diminution of QTc may be noted as the carditis subsides.

J. A. Cosh.


The study reported was based on 16 haemolytic streptococcal infections occurring in forty rheumatic subjects: 34 of the infections were treated with penicillin, the remaining twelve, “ for various reasons” [unspecified] being untreated and therefore regarded as controls. Five of the patients were treated intramuscularly with aqueous benzyl penicillin in divided doses totalling 120,000 to 400,000 units per day. In the remaining patients penicillin was administered by the mouth in the form of buffered tablets of sodium or procaine benzyl penicillin, usually in doses of 1,000,000 units a day. The treatment in all cases was given as soon as possible after the infection and was continued for 10 days.

Recurrence of the rheumatic fever developed during only two of the 34 penicillin-treated infections; in contrast there were six instances of recurrence following twelve untreated infections. The authors conclude that prompt penicillin therapy in streptococcal infections may reduce the incidence of rheumatic recurrences. R. S. Illogworth.


In this valuable article the authors give provisional answers, based on their own observations in 43 cases and the published experience of others, to a number of questions concerning the treatment of rheumatic fever with cortisone and ACTH.

It is stated that fever abates as a rule in 1 to 6 days, but the temperature may not become steady for 2 or 4 weeks. However, the immediate fall in temperature is not to be taken as an indication of the degree of activity of the rheumatic fever. Tachycardia is more persistent, the pulse taking 1 to 3 weeks longer to become stabilized. Arthralgia quickly diminishes, but joint swelling is a little more tenacious. Nodules disappear in 3 to 4 weeks and the erythrocyte sedimentation rate (E.S.R.) becomes normal between the 10th and 31st days of treatment.

Pericardial friction usually disappears in less than a week, though regression of the cardio-pericardial x-ray shadow often takes 2 to 3 weeks. The effect on the endocarditic lesions depends essentially on the initial condition of the heart and on the duration of the acute phase before treatment is started, the authors never having observed regression of the signs of established rheumatic heart disease. On the other hand, they have never seen cardiac signs appear after the first 48 hours of treatment. One may hope that by early institution of hormone treatment, before the onset of carditis or in its early stages, cardiac sequelae may be prevented.

It is considered important to guard against the risk that the excess of adrenal hormones may cause water insufficiency, by restriction of fluid and salt intake, and...
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administeration of mercurial diuretics if necessary. Interruption of treatment for 12 to 24 hours usually secures a prompt diuresis.

ACTH is given in doses of 75 mg. (less for small infants) daily in four regularly spaced injections; whereas cortisol is given by injection every other day. The dosage is not stated. Ideally, treatment should be continued for 2 weeks after disappearance of all clinical signs and terminated by progressive reduction of dosage. In acute articular rheumatism without carditis, or with incipient carditis, it may be given for 4 weeks; in severe cardiac rheumatism it should be continued for more than 2 months.

Kenneth Stone.

Chronic Articular Rheumatism

(Rheumatoid Arthritis)


The case is described of a woman aged 50 with rheumatoid arthritis in whom bilateral epikeratitis with nodular and plaque-like formations of the anterior sclera developed in both eyes. These gradually disappeared with topical cortisone therapy, but a severe recurrence appeared shortly after its cessation, with signs of anterior uveitis and secondary glaucoma. Considerable improvement took place after treatment with cortisone administered systematically. H. E. Hobbs.


The oral administration of cortisone to patients suffering from rheumatoid arthritis produced an effective clinical response in 99 out of 100 cases. In 27 of these the hormone was given by the intramuscular route in the first instance, while in the rest it was administered orally thereafter. In one case which failed to respond to oral administration responded satisfactorily to subsequent intramuscular injection. In about one-half of the cases in which both routes were used effective oral and intramuscular doses were the same, while in the remainder an extra amount, which varied from one-sixth to one-quarter of the intramuscular dose, was required for oral administration. The speed of action was greater and its duration shorter by the oral route and in consequence divided doses were employed. In the 72 patients given cortisone by mouth only initial treatment for a period varying from 2 days to 2 weeks was required to establish the desired suppression of symptoms, the daily dose required ranging from 37.5 g. to 100 g. Subsequently it was found that in 21 per cent. of cases improvement could be maintained on a daily dose of 37.5 g. or even less. The authors prefer to give lower initial suppressive doses than those originally advocated. They stress the need for the very gradual reduction of dosage if a low maintenance level is to be attained without relapse occurring. They state that the patient's needs appear to vary from time to time so that maintenance dosage can never be regarded as permanently established, even after many months of satisfactory suppression. The side-effects observed in this series were no different from those observed in series treated with cortisone by the intramuscular route. In only two cases did gastrointestinal irritation follow the oral administration of cortisone tablets. W. S. C. Copeman.


The results presented in this paper demonstrate that sodium p-aminobenzoate enhances the action of cortisone in the treatment of rheumatoid arthritis. This substance was tried because it is known to inhibit inactivation of oestrogens by the liver; and there is a similarity in chemical structure between cortisone and the oestrogens.

In one group nine patients with rheumatoid arthritis were started on the usual dosage of cortisone acetate until maximum relief was obtained. The daily dose was then reduced to 25 mg. All patients relapsed. Sodium p-aminobenzoate was then given orally, 1-5 g. 2-hourly to a total of 12 g. daily, in addition to the 25 mg. of cortisone parenterally. Relief was again obtained; to approximately the same degree in five cases, somewhat less in three, and slightly greater in one.

In a second group six patients with rheumatoid arthritis were treated from the beginning with 25 mg. of cortisone acetate parenterally and 12 g. sodium p-aminobenzoate daily in divided doses of 1-5 g. 2-hourly. All patients showed improvement comparable to that obtained with cortisone in the usual doses.

Three detailed case reports are given. No undesirable side-effects were observed. Thus by the combined use of cortisone and sodium p-aminobenzoate rheumatoid arthritis can be controlled when the same dose of cortisone alone would be ineffective. Kenneth Stone.


In the 2 cases that have followed Lièvre's original suggestion (Bull. Soc. Fr. Ophtalmol., Paris, 1949, 65, 1256) of carotid-sinus denervation in the treatment of rheumatoid arthritis (in order to stimulate the adrenal cortex) the authors have operated on 32 cases, bilaterally in fourteen and unilaterally in eighteen. In eight there was no improvement, six derived transient benefit, another eight maintained improvement for periods of 6 to 8 months, four showed spectacular improvement, and others, recently operated upon, derived some benefit. There were two deaths.

Local analgesia was used by the authors, who discuss the indications for, and the dangers of, this operation. They conclude that it should be reserved for patients under the age of 50, and should be carried out before irreversible changes have taken place. They find it difficult to lay down any hard-and-fast rule on the advisability of unilateral or bilateral denervation. D. Preiskel.


Serial vasography in cases of primary progressive chronic articular rheumatism of the hand and wrist revealed important vascular changes, the most important of which was an arterial ischaemia. The arteries round
the joints were either narrowed or blocked. To this schaemia the author attributes the wasting of the peri-articular tissues, and the atrophy of the articular cartilage without any noticeable reaction. The calcium content of the bone was normal to begin with, but later on the atrophy of the cartilage was followed by a secondary reorientation of the subchondral bone and by deformity of the edges of the bone.

The observed venous congestion was probably the result of the arterial changes. Comparison of the extensive vascular changes with the slight skeletal changes in the early stages of the disease suggests that the disease is primarily of vascular origin. A. Orley.

ACTH, Cortisone, and Other Steroids


In experiments carried out at University College Hospital Medical School, London, the author found that cortisone given intramuscularly in daily doses of approximately 12.5 mg./kg. body weight had no effect on wound healing in guinea-pigs. In rats it had no dramatic effect either on the healing time or on the quality of the granulation tissue, which in some cases, however, was reduced in quantity. The administration of cortisone in doses of 7.5 mg./kg. daily retarded wound healing. The effect of cortisone on wound formation in rabbits following the injection of leucocytic peptides and of histamine was also studied. Before the injection of these substances the animal was given an intravenous injection of trypan blue: cortisone prevented the leakage of the dye into the tissues. The author suggests that there may be some connection between the subduing effect of cortisone on the formation of granulation tissue and its apparent ability to protect small blood vessels from substances capable of increasing their permeability. If, as seems likely in the case of wound healing in rabbits, cortisone is merely depressing a normal process, its action is most probably to control the degree of reactivity rather than to alter its pattern. Whether cortisone exerts its effect throughout the process of wound healing is not known, but it is evident from the results obtained that cortisone is active in its earliest stages, namely, the stages of hyperaemia and oedema formation. A. G. Riddell.


ACTH and cortisone are known to alter cellular and fibrous-tissue reactions and to restore the serum albumin-globulin ratio. As beryllium granulomatosis shows cellular and fibrous-tissue reactions with hyperglobulinemia a trial was made of ACTH treatment in two cases of this condition. Metabolic studies were carried out, together with respiratory function tests and radiological assessment, and detailed figures for the analyses of blood and urine are given.

ACTH, 100 mg. daily, was administered in the first case for 28 days and in the second for three periods of 5 to 15 days. In both cases there was relief of symptoms and objective (x-ray) improvement during treatment. The development of oedema and emotional instability was noted during treatment. Cessation of hormone therapy was quickly followed by weakness, headache, and pyrexia for a week or two, and there was a return of the physical signs and of the x-ray opacities. The first patient maintained "some improvement" 2 months after therapy was completed, while the second had reverted to his previous condition within a month.

A case of simple silicosis was also treated, the dose of ACTH being increased to 160 mg. daily. In this case, cortisone also was subsequently administered. Symptomatic improvement occurred, with increased exertion tolerance. No changes in the x-ray appearance of the chest were seen, but the patient "remained improved".

Further study is indicated to discover whether ACTH is capable of promoting mobilization and excretion of beryllium from the tissues. It would seem that repeated short courses of ACTH may produce fewer complications.

L. W. Hale.


Evidence has accumulated that ACTH and cortisone can diminish resistance to infection both in experimental animals and man. The mechanisms responsible are not yet clearly understood, but it is possible that the general catabolic effect of the hormones, their inhibitory action upon granuloma formation, and their destructive action upon lymphatic tissues may be involved. The author, having noted that somatotrophic hormone (STH) acts antagonistically to ACTH in these respects, argued that it might be able to increase resistance to infection.

In one experiment, eight rats were given 10 mg. cortisone acetate by subcutaneous injection daily for 12 days; five died before completing the course; these and one survivor had multiple abscesses; all had lost a great deal of weight. A further nine rats, while receiving the same dose of cortisone, were also given 2 mg. STH daily; all survived and their average weight was unchanged. The experiment was repeated over a 17-day period with comparable results. In a second experiment cortisone was replaced by ACTH given subcutaneously in 2-mg. doses six times daily; five out of seven animals given ACTH alone had multiple abscesses, while all of seven given STH in addition remained healthy.

Microscopically, the animals in which there was abscess formation showed many large bacterial colonies throughout the lungs, kidneys, liver, and spleen (and in two cases on the peritoneum and in one on the endocardium) with almost no connective-tissue reaction. Identification of the bacteria has not been completed, and it remains to be established whether STH arrests the growth of the true pathogens or only of those normally non-pathogenic organisms whose proliferation is stimulated by an excess of glucocorticoids.

There is a brief discussion of the significance and possible explanations of these findings. H. McC. Giles.


Cortisone acetate (1.25 mg. daily) was injected into normal rats and into hypophysectomized rats maintained on a constant dosage (0.4 mg. thrice daily) of adrenocorticotropic. The treatment reduced the weight and increased the cholesterol content of the adrenals in the normal rats, but had no such effects in the hypophysectomized animals. This is strong evidence that cortisone...
produces these effects by reducing adrenocorticotropic hormone secretion. This would explain the beneficial results that have been reported (Wilkins, Lewis, Klein, and Roenbeck (1950). Bull Johns Hopkins Hosp., 86, 249), when cases of adrenal hyperplasia are treated with cortisone.

Peter C. Williams.


The author has studied the level of pre-existing antibody and antibody synthesis in patients treated with ACTH and cortisone. He vaccinated 59 patients with a single injection of a mixture of pneumococcal polysaccharides. Of these patients seventeen were treated with ACTH, and twelve with cortisone, and thirty were untreated. The production of mouse protective antibody to pneumococcus Type II was measured. Patients whose pre-vaccination serum neutralized more than 10 MLD of the pneumococci were eliminated from the series. Expressing the neutralizing capacity of the serum as the logarithm of the number of MLD's surviving, the geometric mean of the titre of neutralizing antibody before vaccination was slightly greater in the control group (0-58 log) than in the treated group (0-41 log). After 10 to 21 days the figures were 3-75 log and 5-41 log respectively.

The effect of the titres of agglutinins for typhoid H antigen was studied in five patients with a titre of 1 in 10 or greater. In two the titres became fourfold to eightfold lower during treatment; in three there were no obvious changes. The titres of isohaemagglutinins for erythrocytes of different ABO blood groups were studied in eleven treated patients. In five patients (three receiving ACTH, two cortisone) the titre was fourfold higher during treatment than before. Serum globulin, measured by zinc sulphate turbidity decreased in thirteen out of seventeen patients on ACTH and in six out of twelve on cortisone. The present evidence suggests that the beneficial effects of ACTH and cortisone in the treatment of hypersensitivity states and related diseases are not to be explained by suppressed antibody production.

The author discusses the apparently conflicting results which have been reported concerning adrenal effects on plasma proteins and antibodies in experimental animals and considers them to be due to species differences, the rat seeming to resemble man rather more closely than does the rabbit.

Harold Kaplan.


The authors found that the formation of granulation tissue around turpentine abscesses in the rat is modified if cortisone is mixed with the turpentine (0-5 mg. in 0-5 ml.). In comparison with control abscesses around 0-5 ml. turpentine alone, the granulation-tissue layer was thinner, the fibroblasts were smaller and less regular in formation, and the cellular infiltration was more profuse; vascularization appeared to be unaffected. Further experiments with cortisone-containing abscesses in ischaemic and in denervated tissues showed that these conditions did not materially modify the effects of cortisone on connective tissue outlined above. Although the mechanism of the inhibitory effect of cortisone on connective tissue is unknown, these experiments suggest that it is a direct local action rather than an action on either vasomotor mechanisms or the metabolism of nervous tissues.

B. E. W. Mace.


The 11-oxygenase is known to have an inhibitory effect on many cellular enzyme systems, and there is evidence to suggest that this action is due to reduction in availability of sulphhydryl groups (-SH). Other substances also have this action, notably ascorbic acid through its oxidation product dehydroascorbic acid.

A series of estimations of the sulphhydryl level in blood, in normal subjects and in patients with rheumatoid arthritis, showed that massive intravenous doses of ascorbic acid had no significant effect. The level was also found to be unchanged in rheumatoid arthritis, both before and after cortisone treatment. Another series of experiments was carried out with a hyaluronidase-indian ink mixture containing 75 turbidity units of hyaluronidase in 0-7 ml. This mixture, intracutaneously into the depilated skin of white mice. The hyaluronidase mixture spread further in the tissues than the saline control, but this effect was inhibited after the mouse had given 2 mg. cortisone subcutaneously. Reduced glutathione (G-SH), 40 mg., was then given intraperitoneally; the original or increased skin spread was observed after a further injection of the hyaluronidase-indian ink mixture. A control experiment in which oxidized glutathione (G-S-S-G) was used showed that this had no effect on the cortisone-inhibited skin spread.

B. E. W. Mace.


Determination have been made of the output and concentration of urinary 17-ketosteroids in healthy subjects and in patients suffering from adrenal disease. In a group of ten healthy women between the ages of 27 and 52 years the output ranged from 5-2 to 15-3 mg. in 24 hours, and the concentration from 0-4 to 1-2 mg. per 100 ml. In a healthy woman aged 33 who was observed over a period of 2 years the output varied from 9-8 to 22-5 mg. in 24 hours; and in a group of men with various suppurative conditions the average output was 12-4 mg. and the average concentration 1-3 mg. per 100 ml. Investigation was also made of thirteen patients with Addison's disease; the output of 17-ketosteroids varied from a trace to 2-8 mg. in three patients in whom the disease was due to tuberculosis, and from 2-3 to 11 mg. in four cases of different aetiology. Treatment with deoxycortone did not increase the output of 17-keto steroids in the patients with Addison's disease, but raised the output to normal levels in three female patients with more benign forms of Addison's disease, and to 28-8 and 33-3 mg. respectively in two male patients. Hyperactivity of the adrenals led to increased output of 17-ketosteroids, and values up to 25-9 mg. in 24 hours were noted in two otherwise healthy persons suffering from acne; an output of 33-2 mg. was observed in a hermaphrodite and one of 30-2 mg. in a woman with Cushing's syndrome. The exceptionally high value of 806 mg. in 24 hours, with a concentration of 10-3 mg. per 100 ml., was found in a woman with a malignant adrenal tumour with widespread metastases.

D. J. Bauer.

A trial of “artisone” acetate in patients with rheumatoid arthritis revealed no beneficial effect. The patients were observed carefully, both clinically and biochemically, before, during, and after the administration of the drug, which was given in doses of 100 to 200 mg. daily.

D. P. Nicholson.


This is a report of the case of a female, 39 years of age, who had been under medical care for 17 years, and who in 1947 developed rheumatoid arthritis, for which she was given cortisone in May, 1950. A radiograph of the chest was at that time clear. Cortisone had a good effect, and this was maintained for 4 months; when a relapse occurred in November, further cortisone was given, but was soon discontinued as the patient developed symptoms and clinical and radiological signs of a lesion at the right lung base. She died 2 months later, the radiological appearances being typical of an acute caseous tuberculosis.

Although no necropsy was performed, and although tubercle bacilli were never isolated, the authors consider that the patient died from a rapidly progressive tuberculosis, probably originating from old infective foci in the lungs which had broken down under the influence of cortisone on normal protective mechanisms.

B. E. W. Mace.


Groups of guinea-pigs were sensitized by the subcutaneous injection of 2-5 to 5-0 mg. heat-killed tubercle bacilli suspended with tuberculin. The injected dose of 0-1 ml. of turpentine intradermally was measured after 24 hours. Subsequently a daily dose of 20 to 30 mg. ACTH per kg. body weight was given at 8-hourly intervals for 16 days. At the end of this period and 2 weeks later the skin tests were repeated. It was found that under treatment with ACTH the erythematous area was significantly reduced in size; 2 weeks later it usually had reverted to its original size. - Control groups treated only with saline did not show these changes. The complement-fixing antibody titre was not affected by ACTH; lymphocyte and eosinophil counts were decreased.

In another series, a group of six guinea-pigs received 0-1 ml. oil of turpentine intradermally. This caused an area of edema and induration whose centre was necrotic. When ACTH was given in the same way as in the first series, the size of the central necrotic area remained unchanged, but that of the peripheral area decreased. It is suggested that the major role of ACTH is the suppression of tissue responses to injury. Its influence on antibody formation is regarded as uncertain.

H. Hersheimer.


The May Foundation. 48 mg. of cortisone was injected sc. into each rat. The animal was killed 24 hours later and a positive reaction was seen in all of them. On the 20th day six animals which were killed to serve as controls were found to have granulomas. On the 20th day two of the remaining 42 animals were divided into five groups: ten untreated controls, and four groups of eight each to be treated once daily with 6 mg. cortisone, 2 mg. streptomycin, 2 mg. cortisone, and 2 mg. streptomycin combined with 2 mg. cortisone, respectively. There was also a fifth group of six healthy animals to be treated with cortisone, and a sixth group to be treated with cortisone and streptomycin combined. Treatment in all cases continued for 62 days, when survivors were killed.

The results showed that administration of cortisone or cortisone with streptomycin was not beneficial, in that animals so treated failed to gain weight. Cortisone treatment also led to reduction in size of the tuberculin reaction and also in the number of reactions with the use of both drugs. Post-mortem examinations showed that 6 mg. streptomycin once daily for 62 days caused a marked reversal of the progressive disease presumed to have been present when treatment was started. Administration of 2 mg. cortisone resulted in only partial inhibition of the disease. Of the group of eight animals given streptomycin with cortisone, six did not show even this partial improvement. The extent of the lesions in the animals given cortisone alone was comparable to that in the untreated controls.

Microscopically, the lesions in the animals treated with cortisone only were similar to those in the untreated animals. In those treated with 6-mg. doses of streptomycin the lesions seemed to be healing, whereas with 2 mg. there appeared to be a definite retardation of the disease. In the animals treated with both drugs the lesions were comparable in extent and appearance to those in the controls and in those given cortisone alone. The main effect of cortisone seemed to lie in preventing restriction of the disease by inhibiting fibrosis. Experiments in vitro showed that cortisone neither interfered with nor enhanced the bacteriostatic effect of streptomycin.

R. B. Lucas.


The effects of treatment with ACTH were studied in fifteen patients between the ages of 13 and 61 suffering from myasthenia gravis of 1 to 17 years' duration. Each patient received 25 mg. ACTH 6-hourly for 5 days, in addition to neostigmine and other therapy. Electromyographic studies and acetylcholine-synthesis determinations were carried out daily. During the last 2 days of administration of ACTH and for a few days thereafter a gradually increasing disability occurred, consisting mainly of asthenia, malaise, headache, and insomnia, and one patient with bulbar signs died on the third day of treatment. In the remaining fourteen cases improvement began during the first week after the last injection and continued for a few weeks. Improvement included increased well-being and increased work

A series of forty patients with chronic ulcerative colitis (severe in 22 cases) were treated at the Frank Billings Medical Clinic, University of Chicago, with ACTH after having been under a period of observation. The ACTH treatment was preceded and followed by a period in which saline, which was represented to the patient as being ACTH, was injected. The total dosage of ACTH ranged from 1 to 3 g., the largest being 7-92 g. in 126 days.

Clinical response was good in 27 cases—feeling of well-being increased, appetite improved, stools decreased in bulk and frequency, and fever abated; only four patients showed no improvement. The appearance of the mucous membrane improved greatly in twenty cases and less obviously in fourteen others; edema and friability diminished, but granularity persisting. In no case was a completely normal mucosa seen, and the radiological appearances remained abnormal. Laboratory investigations reflected this improvement. The erythrocyte sedimentation rate fell, faecal lyzyzome content diminished in four patients, and erythrocyte cholinenesterase content fell. In the dosage used ACTH produced side-effects (such as hypopotassaeimia) in four cases, and withdrawal symptoms of malaise, fever, and muscle cramps occurred in almost half the total. The results were considered good, long courses of over 6 weeks being most effective, but the eventual relapse of twenty out of 36 originally benefited suggests that the effects of ACTH on ulcerative colitis is only temporary, although the relapses seemed to be of reduced severity.

K. Gurling


The authors have carried out comparative studies of the clinical and physiological effects of cortisone given orally and by intramuscular injection. In general they found that oral cortisone has a quicker, more profound and less prolonged action than the same dose given intramuscularly.

The physiological activity of cortisone was estimated by the fall in circulating eosinophils. When 50 mg. was given orally there was a marked reduction in the eosinophil count after 4 hours, the count returning to normal within 24 hours (intravenous cortisone has a similar effect). When 50 mg. was given intramuscularly little change in eosinophil level could be detected after 4 hours; there was a fall later, which was still demonstrable at 24 hours. From the results presented it would seem necessary to give cortisone by mouth every 6 hours to maintain a useful level of activity.

Trials with 'Compound F' and its acetate given by mouth indicated that these were more active by this route than was cortisone, and that the metabolic rate of Compound F, particularly of free Compound F, was shorter. A further series of experiments showed that oral cortisone caused immediate sodium and chloride retention and potassium excretion in Addison’s disease, and that this effect disappeared soon after discontinuance of the drug. This was in contrast to the delayed effects of intramuscular administration of cortisone. It is pointed out that...
patients receiving oral cortisol are not protected, after withdrawal of the drug, from a period of adrenal insufficiency. However, the adrenal glands react to a series of injections. The authors also quote a case in which small doses of cortisol have been given orally to suppress adrenal hyperfunction in a case of adrenal virilism, with successful results.

Clinical investigations showed that a combination of deoxycorticosterone acetate (DCA) and cortisol was a more satisfactory treatment for Addison's disease than DCA alone, as appetite, weight, and muscle strength were improved, anaemia was corrected, and hypoglycaemic complications were prevented. The successful oral use of cortisol to relieve an acute exacerbation of gout and also in a patient with chronic rheumatoid arthritis and pulmonary sarcoidosis is described.

The authors consider that cortisol is as effective orally as by intramuscular injection, but point out that the fact that it is so effective enhances the potential dangers of its indiscriminate use.

B. E. W. Mace.


In this investigation 27 male rats approximately 300 g. in weight were given a high-fat, low-carbohydrate diet, and seventeen of them received continuous injection of ACTH in doses of 10 to 40 mg. daily for up to 21 days or until the animal became moribund. A control group of ten rats was given continuous injection of saline only for the same period.

Of the seventeen animals treated with ACTH ten were moribund within 12 to 20 days. All of them showed glycosuria on 2 or more days. This was only temporary in most cases, and disappeared while treatment was continued. Marked acetonuria occurred on 2 or more days in fourteen of the animals. All seventeen rats developed a negative nitrogen balance, but the peak of nitrogen excretion was not sustained, and in some cases fell to control values, during continued injection of ACTH. The rats lost weight rapidly during the first few days, the weight loss being closely related to the values for urinary non-protein nitrogen; the weight of the animals then remained relatively stable.

At necropsy three rats had diffuse infections involving the lungs, pleura, heart, liver, kidneys, and gut, and twelve had ulcers in the pyloric portion of the stomach, varying from multiple tiny ulcers to a few large deep ulcers which almost penetrated the mucosa and from some of which there was considerable loss of blood. Of the treated animals three had white spots penetrating the surface of the heart muscle, and eleven showed renal lesions consisting of grey patches penetrating the cortex, with occasional tiny nodules of hypertrophic tubules. None of the changes described was seen in the control animals.

Previous studies with cortisone had shown that doses of 10 mg. daily were necessary to produce effects comparable with those of continuous injection of ACTH, suggesting that the adrenal cortex of the rat can be made to secrete the equivalent of this amount of cortisone per day. The authors point out that the biological effectiveness of ACTH is much greater when it is given by continuous injection than when it is given intermittently.

Robert de Mowbray.
with ACTH the changes were interpreted as due to stress, since the dose of ACTH was inadequate, or the time-interval after treatment too long, to account for them.

After prolonged administration of cortisone there was atrophy of the zona fasciculata and zona reticularis, while the zona glomerulosa appeared to have increased in width and its cells were of normal size. Sudanophilic material was present, though in reduced concentration. The accumulation of lipid in conjunction with the adrenals was regarded as evidence of storage of adrenal steroids or their precursors. The resemblance of these changes to those seen in cases of hypopituitarism suggests that cortisone induces adrenal cortical atrophy by suppressing the secretion of ACTH.

In two patients who died 17 and 51 days respectively after the last dose of cortisone there was evidence of a return to normal of cell size and lipid pattern, indicating that the cortical atrophy is reversible. Robert de Mowbray.


The 17-hydroxycorticosteroids in the blood of normal subjects and patients with various diseases were assayed by extraction with chloroform-ether, partition between 70 per cent. ethanol and hexane, chromatography on magnesium sulphate, and analysis by colorimetry on reaction with phenylhydrazine in sulphuric acid. The concentration in normal subjects was 4 to 10 μg. per 100 ml. of blood, and normal values were found in patients with rheumatoid arthritis and a variety of other diseases of varying severity; the only abnormal values found were in three cases of Addison's disease, in which where no 17-hydroxycorticosteroids were detectable in the blood, and in five dying patients whose blood content 15 to 50 μg. per 100 ml. Paper chromatography of the material showed that it consisted mostly of Compound F; Compound E was not present but Compound S might be. Arteriovenous differences in concentration of 17-hydroxycorticosteroids, if present, were less than the error of the method (+20 per cent.) even in areas of acute inflammation. The blood level was increased by the injection of ACTH, but the effect was short-lived unless the hormone was given by intravenous drip. The increased levels found in the dying patients were about equal to those produced by the intravenous infusion of 15 mg. ACTH during 24 hours. Peter C. Williams.


In this study of the eosinopenic response to cortisone and ACTH the number of circulating eosinophil leucocytes was estimated in a counting chamber by a modification of Dungar's method in four healthy male subjects, aged 32 to 43, under normal working conditions. Duplicate readings differed by +5 per cent. for counts of 100 per c.mm. or over, though with very low counts the error was greater.

Morning counts were made between 9.30 and 10 a.m. They varied by up to 300 per cent. on different days in any one subject, and differed considerably as between one subject and another. On control days the eosinophils were consistently 2-hourly and the mean fluctuation throughout the day was no more than 10 per cent. of the morning count in any one subject, though occasionally there was an increase or decrease of about 40 per cent. On other days ACTH or cortisone, in single doses of 2.5 to 100 mg. intramuscularly or 6.25 to 100 mg. orally respectively, was given immediately after the morning count. The fall in eosinophil count began within 2 hours and was pronounced at 4 hours. With the higher doses the count continued to fall at 6 hours and was still low at 8 hours, whereas with the lower doses the count increased again at 6 hours and tended to return to the morning level or above after 8 hours. The 4-hour and 6-hour counts therefore gave the most information. Repeated injections of the same dose did not give strictly comparable curves of eosinophil response, which was not considered surprising, in view of the spontaneous fluctuations of the eosinophil count already described.

The responsiveness to ACTH and cortisone differed considerably as between the four subjects, and the response to ACTH differed from the response to cortisone in two of the subjects. The two who gave satisfactory eosinopenic responses to small doses of both hormones also showed a wide range of fluctuation in their morning counts, whereas the other two who were less responsive, showed smaller variations in their morning counts.

An acute febrile stress was induced by 10 ml. T.A.B. intravenously in two patients with rheumatoid arthritis and also in the four subjects of this study. The fall in eosinophil count was in each case about equivalent to that which followed a single injection of 25 mg. ACTH, though it was of longer duration. In three cases of panhypopituitarism there was a greatly exaggerated and prolonged eosinopenic response to oral cortisone. Robert de Mowbray.


Ten normal subjects were given large doses of sodium salicylate by mouth; four received 4 g. and six received 6 g.; two similar subjects acted as controls. Eosinophil counts were made immediately before the dose, then at hourly intervals for 6 hours, and finally 8 hours afterwards. Counts were also made on 6 samples of urine 1 hour after the first dose. By the direct eosinophil method, using Dungar's fluid; at the same intervals of time the plasma salicylate was estimated by Van Cauwenberge's method. The urinary uric acid: creatinine ratio was calculated every 2 hours.

In agreement with the observations of Meade and Smith (Lancet, 1951, 1, 773) the authors found no significant decrease in the number of circulating eosinophils during the first 4 hours following salicylate administration. However, a marked decrease was observed from the fourth to sixth hours. Different dosage and different time of observation would therefore account for discrepancies in the reports from the two laboratories. The delayed decrease in the amount of circulating eosinophils when salicylate is administered by mouth seems to be due to the slowness of intestinal absorption of the drug.

The urinary uric acid: creatinine ratio which increased significantly by the second hour, an event which, like eosinopenia, is indicative of oversecretion of cortical factors. Nancy Gough.


Endogenous cortisone excretion was estimated by comparing the fall in the eosinophil-cell count (in
adrenalectomized mice) produced by urinary extracts, with that produced by cortisone acetate. Cortisone and Compound F are the only known substances that will produce such a fall, and as both have been isolated from urinary extracts prepared in a similar way the test is presumably specific. The extract will probably contain an unknown proportion of Compound F but the activity is expressed as if it were all due to cortisone. The volume and nature of the solvent are important, as slight variations in the procedure affect absorption from the subcutaneous site and consequently the eosinophil-cell response; 0.5 ml of 20 per cent. propylene glycol was used in the present tests. Each urine sample was tested by injection into three mice and this requires the urine excreted during 12 to 48 hours. The methods used have already been described (Cope, C. L., Brit. med. J., 1951, 1, 271; Abstracts of World Medicine, 1951, 10, 72).

The daily excretion was 40 to 120 μg. in the absence of stress, and 170 to 320 μg. during "medical" stress or during late pregnancy. When patients were injected with 100 mg. ACTH daily there was a progressive rise to levels of 250 to 650 μg. per day. The injection or oral administration of cortisone increased the output within a day, but the extra activity in the urine only represented 0.2 mg. per cent. of the exogenous material. The cortisone output was subnormal in seven cases of Addison's disease and in four of panhyopituitarism; it never amounted to more than 70 μg. per day, and in six cases was indetectable. Ephedrine given orally (65 mg. thrice daily) to one patient doubled the cortisone output, but a lower dosage (32 mg. thrice daily) was incapable of maintaining an increased rate produced by ACTH treatment. It is concluded that the test is reliable enough to "reveal the more gross variations of cortisone output in man" and is probably a better index of adrenal function than the patient's own eosinophil count or the chemical estimation of reducing steroids in the urine. Cases are discussed in which these tests did not agree with the rate of cortisone excretion. Peter C. Williams.

**Treatment of Hemorrhagic Shock with Cortisone and Vitamin B12.** HOWARD, J. M., and DeBAKEY, M. E. (1951). Surgery, 30, 161. 2 figs, 5 refs. The authors observed the effect of cortisone and vitamin B12 on haemorrhagic shock in dogs, which were bled until the blood pressure fell to 30 mm. Hg, and then maintained at that level by subsequent small bleedings and small transfusions until a state of irreversible shock was reached; this point was indicated by the inability of the shocked animal to maintain its blood pressure at the level of 30 mm. Hg despite repeated transfusions. Under these conditions it was demonstrated that neither cortisone nor vitamin B12 had any significant effect upon the course of haemorrhagic shock.

**Thromboembolic Complications associated with ACTH and Cortisone Therapy.** COCHRAN, S. W. (1951). J. Amer. Med. Ass., 147, 924. 7 refs. The author, working in the Presbyterian Hospital, New York, has found that 28 patients out of 700 receiving ACTH or cortisone therapy had one or more thrombo-embolic complications, with a total of forty episodes. Increased coagulability of the blood had previously been noted in patients treated with ACTH and cortisone, and the purpose of the analysis of the clinical data of these 28 patients was to determine if possible the relationship between the thrombo-embolic complications and the hormone therapy.

Of the 28 patients, 21 (75 per cent.) were aged between 40 and 79, the age range in which thrombotic disease is usually encountered. Of the forty thrombo-embolic episodes, nineteen occurred in patients confined to bed, eight in semi-ambulatory patients, and thirteen in ambulatory patients. Most of the patients were suffering from diseases in which cortisone or ACTH therapy is usually considered to be of some value, twelve being under treatment for rheumatoid arthritis. Some of the patients, however, had septic conditions which might predispose to thrombotic complications. Thrombo-embolic episodes occurred equally in the ACTH- and cortisone-treated cases; nineteen of the 28 patients had received cortisone or ACTH for 3 weeks, others for longer periods up to 9 months, before the onset of the thrombosis. In eight patients, the first thrombo-embolic episodes occurred during hormone therapy, and in ten after it has been discontinued; in seven of these ten they occurred within one week of stopping the treatment. Thrombo-embolic complications occurred more frequently in those receiving the higher doses of cortisone or ACTH.

The author points out that comparative statistics which would indicate the incidence of thrombotic phenomena in a similar group of patients are not available, but he considers nevertheless that the occurrence of forty thrombotic episodes in 28 patients from among 700 patients receiving cortisone or ACTH therapy is greater than would be expected. C. E. Quin.

**Effects of Cortisone on the Mechanism of Increased Capillary Permeability to Trypan Blue in Inflammation.** MENKIN, V. (1951). Amer. J. Physiol., 166, 509. 3 figs, 23 refs. The local increase in capillary permeability normally resulting from the intradermal injection in rabbits of inflammatory exudates obtained by the intraperitoneal or intraperitoneal injection of various irritants into dogs and rabbits was shown to be inhibited when the exudate was mixed with adrenal cortical extract or with cortisone in the case of alkaline exudates, whereas no such inhibition occurred with acid exudates. That the effect of cortisone and adrenal cortical extract is not determined simply by adding lactic acid to the alkaline exudate and sodium hydroxide to the acid exudate before injection without altering the results obtained. It is therefore suggested that "concomitantly with the developing acidity in the later phase of the inflammatory reaction, there is liberated in abundance a factor, other than leukotaxine, capable of sustaining the increase in capillary permeability throughout the length of the acute inflammation." The name "exudin" is proposed for this factor, which appears to supplement leukotaxine. The relationship of exudin to physiological homeostasis is discussed. Kathleen M. Lawther.

**Effects of ACTH on the Mechanism of Increased Capillary Permeability to Trypan Blue in Inflammation.** MENKIN, V. Amer. J. Physiol., 166, 518. 3 figs, 8 refs. The increase in capillary permeability induced by acid inflammatory exudates containing exudin is inhibited by ACTH which, in contrast to cortisone, fails to suppress the like action of leukotaxine. Cortisone on the other hand is ineffective against exudin. It is therefore suggested that the corticosteroids of cortisone and ACTH would seem to be a more effective means of restricting acute inflammatory exudation of acid than either alone,
because of the presence of some leukotaxine and much exudin in acid exudates. The possibility of more effective therapy for rheumatoid conditions is discussed in the light of these findings. Kathleen M. Lawther.


An experimental study of wound healing in dogs showed that cortisone (Compound E) administered subcutaneously (2 mg./kg. body weight) had no demonstrable effect on the healing of clean wounds. This contrasts with the observations of other workers on granulating wounds, where ACTH may retard the healing process.

Guy Blackburn


The authors, working in the Department of Medicine of the University of Virginia, have investigated the influence of ACTH and cortisone on the strength and histological characters of healing experimental abdominal wounds in male albino rats of the Wistar strain maintained on a standard laboratory diet. An incision was made through all the layers of the abdominal wall in the midline and sutured in two layers. Animals were killed at 2-day intervals up to 12 days after operation, and strips of tissue 1 cm. wide were cut transversely across the wound and their tensile strength measured in grammes. The animals were divided into five groups, which were treated as follows:

(1) no treatment before or after operation;
(2) injection of 0-5 ml. saline twice daily from 2 days before operation;
(3) bilateral adrenalectomy performed 1 week before operation, 0-85 per cent. saline being given in drinking water;
(4) 0-5 or 1-0 mg. ACTH injected intramuscularly 6-hourly from 3 days before operation;
(5) 3-0 mg. cortisone injected intramuscularly twice daily from 2 days before operation.

Healing, as shown by tensile strength, was normal in Groups 1, 2, and 3, and also in animals receiving 2 mg. ACTH daily. When 4 mg. ACTH was given daily a moderate retardation of healing occurred. In Group 5 there was marked retardation of healing. Histological examination revealed delay in formation of granulation tissue in the animals of Groups 4 and 5, though the effects were less striking in the latter. It was also noted that proliferation of blood vessels was abnormal in Group 5, sharply delimited focal groups of capillaries being observed at the healing surface of the wound. A relatively large, round, clear cell with apparent vacuolization was also observed at the healing surface in Group 5. It resembled the "foam cell" (Geitlerzelle) of the central nervous system, and was absent in sections from control animals and those treated with ACTH. C. E. Quin.


This article consists, firstly, of a résumé of the known effects of cortisone and ACTH in rheumatic and non-rheumatic affections, and, secondly, of a discussion of the problems that arise from their use. Possible modes of action are suggested for some of the conditions in which these hormones are known to be effective, it is pointed out that they never strike at the root of a disease, but only suppress, temporarily, the normal reactive processes of the organism (except in adrenal insufficiency). The authors discuss the problems of relapse and of adrenal hypofunction, after cessation of treatment, and the dangers arising from hyperadrenalism and from the masking of signs of infection.

After a survey of the respective indications for ACTH and cortisone, the authors conclude that cortisone will be more widely used; while the treatment of acute illness is effective, often spectacularly so, that of chronic states is, as yet, difficult to assess. B. E. W. Mace.


A procedure is described, a modification of that originated in Amsterdam by Dingemanse and her colleagues (J. clin. Endocrinol., 1946, 6, 535), which enables qualitative as well as quantitative studies to be made of the urinary 17-ketosteroids. The method only requires 0-3 mg. ketosteroid, which is the quantity contained in a 3-hr sample of normal urine.

The urine is hydrolysed and extracted either at the same time with toluene or later with carbon tetrachloride or ether. The extract is washed with alkali and the ketonic fraction separated with Girard's reagent P, dried, and redissolved in benzene. The ketosteroid content of this solution (and in subsequent fractions) is determined colorimetrically by the Zimmermann reaction and the appropriate dilution made, containing about 0-3 mg. 5 ml. benzene, for chromatographic fractionation.

This solution is percolated through an alumina column and eluted in forty separate fractions by the addition of solutions of methanol in benzene, rising progressively from 0-05 per cent. to 0-5 per cent., and finally of absolute methanol. When the amounts of ketosteroid (expressed as a percentage of the total) contained in successive fractions are plotted graphically, the graph has a characteristic shape with six major peaks and one minor. The positions of these corresponds with the positions occupied by various pure steroids subjected to the same procedure. The addition of pure steroid to a urine extract heightens the peak at its characteristic position, but does not otherwise affect the shape of the graph. Almost identical curves are obtained from the same individual at different times or from the same sample of urine subjected to different conditions of preliminary hydrolysis and extraction. Warnings are given regarding the preservation of the alumina and maintenance of constant dimensions in the column, which are essential, as non-ketonic materials cause alterations in the form of the graph. It is advisable to use the same amount (0-3 mg.) of ketosteroid for each fractionation and quantities less than 0-27 mg. yield separate fractions too small for colorimetric determination.

Individual values and mean curves are given for six normal men and four normal women in which the two curves are generally similar, but men tend to excrete proportionately more ketosteroid at Peaks II and VI (Fractions 6-7 and 34-35) and women at Peak IV (Fractions 17-25). Very
Neural Control

high total ketosteroid excretion was found in five cases of congenital adrenal hyperplasia and was associated with abnormally high values at Peak III and low values at Peak IV, whereas in another case, which was probably not congenital, Peak III was normal, but an abnormal peak was present in Fractions 8-12. In two cases of burns, one of acute peritonitis, and one of "inflammatory breast cancer", abnormal curves of the same general type were obtained, suggesting that there is a qualitative as well as quantitative change in adrenal metabolism in conditions of stress, and that this resembles that due to pathological hyperplasia. Other cases of malignant disease gave abnormal curves of different types, but normal curves were also recorded. Administration of ACTH to two boys produced curves which differed in the two cases and on different occasions, providing evidence of variation in adrenal responsiveness. Since these abnormal curves are present in men and women to the same extent, it is fair to assume that they indicate changes in adrenal, rather than gonadal, activity. Peter C. Williams.


The authors have studied the effect of ACTH given intravenously in two subjects by means of the fall in eosinophil count and the rise in 17-ketosteroid excretion. To one subject ACTH was administered by drip transfusion over 24 hours every 5 days, observations being made with doses of 0.2-5, 5, 10, 20, 40, 80, and 160 mg. A dose of 5 mg. in 24 hours resulted in almost total disappearance of eosinophil, leucocytes, and the 17-ketosteroid excretion was significantly increased. A 10-kg. dose caused a rather greater 17-ketosteroid excretion, but with larger doses than this the excretion of significantly greater amounts did not occur. The eosinophil count and 17-ketosteroid level returned to normal the day after transfusion, except that when doses of 80 and 160 mg. were used the effect was partly sustained for a second day. ACTH given intramuscularly, 20 mg. every 6 hours, produced only a slight effect on eosinophil count and 17-ketosteroid excretion.

To the other subject a fixed amount (20 mg.) of ACTH was given by intravenous drip, but the length of time taken to give this was varied from 1 minute to 24 hours. It was shown that the full effect was obtained only when the ACTH was given for 12 or 24 hours. These results suggest that there is a minimum dose of ACTH (5 to 10 mg.) which, given intravenously over 24 hours, will produce a maximum degree of adrenal cortical stimulation; that larger doses are no more effective and therefore wasteful; and that much of the physiological activity of ACTH is destroyed when given intramuscularly. B. E. M. Mace.


ABSTRACTS


Other General Subjects


The authors describe five new cases of periosteal dysplasia. The clinical features of each of the cases are briefly discussed and the morbid anatomy and histology of two are described in detail. A general clinical and radiological picture is then presented.

There was no relevant family history. At birth the infant had a small body but a large head, not hydrocephalic in type. The cranial vault had retained its cartilaginous consistency and was parchment-like to palpation. The face was normal except for a parrot-like nose. Proximal limb segments were curved, thickened, and deformed. Extremities were normal in size and shape. The thorax was deformed and the sternum projected forward, while the ribs showed signs of old and recent fractures. The bones, though bulky, were pliant, the joints lax, and the muscles hypotonic. Radiologically, the cranial vault was not ossified. The shafts of the long bones were thickened, widened, and made bulky as a result of numerous intra-uterine fractures, but the epiphyses appeared normal. There was
no visceral or mental abnormality, but immobility was striking, with inability to raise the head or move the limbs. New fractures appeared without apparent reason. The skull became flattened posteriorly and enlarged transversely, and the fontanelles remained large. Histologically, the periosteum was fibrous and thickened, while in the subperiosteal layers ossification was poor and disorganized. At the site of fractures the cartilage was thicker and more active, as though conditions for ossification were more favourable. In three cases death occurred in the first year, one patient was still under observation at one year, and one was alive, a deformed dwarf, at six years.

The condition described, claimed by Porak and Durante to be a disease entity, is compared with achondroplasia (Lobstein’s disease). The authors conclude that only genetic studies and embryological researches will decide whether the two conditions are quite distinct or simply variations of the same genetic fault.

J. M. Alexander.

Neurogenic Factor in Rheumatic Inflammation.

It is suggested that at the site of any referred pain the release of a “pain substance” may set up all the signs of inflammation, with hyperaemia, exudation, joint effusion, and other changes, and thus provide a new primary site for further reflex spread. Various examples are given both of cases of synovitis cured by treatment of a remote primary focus and of production of synovitis by distant trauma. Some are surprising: for example, an effusion in the left knee of a patient with rheumatoid arthritis 2 days after aspiration of the right knee is attributed to reflex causes. Traumatic primary foci are included in this theory, but the fact that they do not spread is not explained. The author does not claim that neurogenic factors are the sole means of spread of rheumatic inflammation, but his argument that they play a predominant part is not convincing.

H. F. Turney.

Experimental Determination of the Hypertensive Diathesis in Man.

To determine whether abnormally large quantities of antibody are produced in response to antigenic stimulus the authors injected 1 ml of blood of a heterologous group into a series of experimental subjects and tested their response by assessing the titre at which the donor’s erythrocytes were clumped by the recipient’s serum at intervals of 1 or 2 weeks. The chosen subjects were a group of medical students and a small group of patients suffering from such conditions as rheumatoid arthritis, inactive rheumatic fever, and disseminated lupus erythematosus.

The authors found that two out of 25 medical students responded with abnormally high agglutinin titres. Among the patients, one suffering from lupus erythematosus, one with erythema nodosum, one with acquired haemolytic anaemia, and three with inactive rheumatic fever, reacted with an unusually high antibody response, but none of three patients suffering from rheumatoid arthritis showed an abnormal response.

The authors conclude from this preliminary work that a small number of both normal subjects and patients suffering from certain diseases have an immunological hyperactivity; they point out, however, that further confirmatory work is needed.

W. Tegner.


Selye’s theory of the “General Adaptation Syndrome” holds that the responses to “stress” may be a pathological on one hand and that an absolute or relative excess of secretion of mineralo-corticoids, the antagonists, is for the administration of large doses of desoxycorticosterone. This article is a discussion of this point, and of its application to inflammatory arthritis in man.

The following questions are raised:

(1) Is desoxycorticosterone a naturally occurring adrenal steroid? Is it present, in minimal quantity, in adrenal tissue, but has never been isolated from adrenal venous blood? It is possibly only present as a precursor of another steroid.

(2) Is desoxycorticosterone not a naturally occurring steroid, is it possible that it is formed in significant quantities in the tissues from a more fundamental substance? This remains a hypothesis, as there is little experimental evidence. Present methods of estimation of the rate of excretion of steroids are unsatisfactory and unreliable.

(3) Tests of adrenal function in rheumatoid arthritis. The work of the authors has not shown any adrenal dysfunction.

(4) Can desoxycorticosterone be shown to play a part in the production of human arthritis, from the result of treatment with this substance? Patients with Addison’s disease, when treated with DOCA and salt, do not develop rheumatic symptoms; in this case the gluco-corticoids, antagonists, are absent. With the normal adrenal function, DOCA, even in high doses, does not cause any form of rheumatism. Deproteinized chloride, effective in producing arthritis in Selye’s DOCA-treated animals, has no effect on human polyarthritis.

(5) Is it possible that the normal regulation of adrenal secretion can be modified to produce a hyper hormon al or dys hormon al state which would be the cause of the diseases of adaptation? Mayer’s theory, for which there is considerable evidence, suggests that this modification is immediate and exact: stress results in increased utilization of adrenal steroids, and the hypophysis immediately increases its output of ACTH to maintain the normal corticoid level. Hypercorticism and dyscorticism thus do not occur, and a theory demanding these states as a basis for the diseases of adaptation is difficult to maintain. Hypertrophy of the adrenal cortex is a usual finding in these diseases, but this is no evidence of abnormal adrenal function.

[B. E. W. Mace.]


A two-year-old boy after having been given 0.15 g. of an antihistaminic, β-dimethylaminobenzohydroxyl ether, hydrocholate, died in status epilepticus. G. M. Findlay.