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 difficulty in recognizing mitral diastolic murmurs in the presence of tachycardia is well known. In order to prolong diastole, "phenylephrine" hydrochloride was given in doses of 0.25 mg. intravenously in children. This drug raises the arterial pressure in 2 minutes, and the pressure returns to normal in 4 to 8 minutes. The pulse rate falls by 36 beats per minute on the average, and the slowing lasts for 3 to 4 minutes. During this phase murmurs are intensified, vanished murmurs may reappear, and murmurs hitherto undetected may be brought out.

Of 64 patients, one complained of occipital headache and one of substernal oppression after the injection. The others had no symptoms. Accentuation of murmurs might outlast the effects on pulse and arterial pressure and might possibly be related to changes in stroke volume or other haemodynamic consequence of the drug.

J. McMichael.


The treatment of 75 children suffering from rheumatic carditis is described. Digitalis and allied drugs were used, and were given in larger doses than is usually considered appropriate to the age of the patient. From 0.09 to 0.24 g. of digitalis leaf was given daily, if necessary per rectum in 15 ml. of 30 per cent. glucose solution. The dose was reduced to one-half, then one-third as the effect of the drug appeared, and treatment was continued for 7 to 14 days or even 1 to 2 months in severe cases. Strophanthus was usually given before treatment with digitalis, and the two drugs were never used together; 5 to 10 minims (0.3 to 0.6 ml.) of the tincture was given daily for 10 to 30 days. Adonis vernalis was also given in some cases. In severe cases where digitalis was not fully effective, hypertonic glucose was given intravenously (15 ml. of 40 per cent. solution) and the patient was placed on a milk diet before giving digitalis. The diet had a diuretic effect which appeared on the third day, and diuresis was also produced by giving "mercusal" in doses of 0.6 to 2.0 g. daily for 4 to 5 days. Severe cases were treated in the open air in summer and sometimes also in winter. Of the 75 patients, eighteen were in the acute stage of the first attack; myocarditis and endocarditis were present in all, and pericarditis in twelve cases. Ten died, four improved but relapsed later, and four were discharged well. Digitalis was often ineffective, and strophanthus was used instead. A further 26 patients were suffering from relapses; mitral insufficiency was present in all, and aortic insufficiency in eight. Here also strophanthus was often more effective than digitalis. Of these 26 patients, sixteen were discharged improved and six died.

The remaining 31 patients were suffering from relapses of lesser severity. The disease was in all cases of 7 to 9 years' standing, and valvular damage was more marked; there were twenty cases of mitral stenosis and thirteen of tricuspid insufficiency. A good effect was obtained with full doses of digitalis, and as much as 0.32 g. was given daily in exceptional circumstances. Ten patients died; eight were discharged improved but relapsed later, and improvement was permanent in the remaining thirteen.

D. J. Bauer.


Chronic Articular Rheumatism

(Rheumatoid Arthritis)


Involvement of the hip-joints in rheumatoid arthritis is not commonly seen, but the authors found the incidence to be at least 10 per cent. A study of forty such cases (32 women, eight men) at Aix-les-Bains suggested that
the disease, usually in a severe form, had at the time of investigation, been present for a minimum period of 5 years. Four stages are described in the evolution of rheumatoid arthritis of the joint beginning radiologically, with narrowing of the upper and inner part of the intraarticular space and ending with deformity of the femoral head and acetabulum, with displacement of both in an upward and inward direction. Arrest may take place at any stage, with development of bony sclerosis; bony ankylosis apparently never occurs.

The importance of early recognition is stressed, and one physical sign which may help to distinguish the condition from osteo-arthritis is mentioned—flexion of the hip is limited at an early stage.

D. Preiskel.


The salicylates have been the drugs of choice in the treatment of rheumatic disease for more than 75 years, and various combinations have been tried. The synergistic action of p-aminobenzoic acid (PABA) and sodium salicylate was discovered in 1946; the blood level of the latter could be increased by from 2 to 5 times by adding an equal quantity of the former. The "spreading factor", hyaluronidase, is supposed to be inhibited by salicylates; this is important because hyaluronic acid is present in abundance in all body tissues subject to rheumatic disease, and the beneficial action of salicylates is due, it has been suggested, to this inhibition. As free hyaluronidase cannot be demonstrated in the blood or synovial fluids of patients with rheumatic disease, the index used is the titre of anti-hyaluronidase in the serum. The authors chose 27 cases of active rheumatoid arthritis for their study, observing the effects of salicylates alone, salicylates with PABA, and PABA alone. The mere raising of the blood salicylate level in rheumatoid arthritis does not appear to give greater relief from pain. The authors also found that the anti-hyaluronidase and antistreptolysin titres and the erythrocyte sedimentation rate were not significantly affected. Clinically, therefore, the addition of PABA offers little advantage in the treatment of rheumatoid arthritis.

D. Preiskel.


Five patients suffering from a severe form of rheumatoid arthritis were subjected to the operation of denervation of the adrenal glands by section of the great splanchnic nerve. Ordinary therapeutic measures had proved ineffective in these patients. All five were cases of long duration, most of the joints being affected; two patients were bed-ridden and two could just walk with the aid of crutches.

In all patients there was clear remission in most of the affected joints within 4 days of the operation. Within 8 hours joint pain at rest had disappeared and sleep improved. Walking was resumed within 10 to 12 days. Improvement in joints with severe destructive lesions did not last more than 30 to 40 days; in joints without much bone destruction relief was more prolonged.

In assessing the biological effects of denervation, the authors make allowance for the "stress" effect on the adrenals of the operative trauma. After operation in four control cases hyperglycaemia was observed, but did not last more than a few hours. After the denervation operation hyperglycaemia persisted for some 3 days. An eosinopenia observed after the control operations was followed by rapid rise to normal before the third day. After the denervation operations eosinopenia persisted for 30 days or more. The authors conclude that denervation causes a hypersecretion of cortisone, perhaps due to cortical vasodilatation.

Two patients in whom joint pains had returned after operation were given injections of ACTH. No beneficial effect was observed; in fact, the less severely affected joints became more painful. On the other hand, cortisone in unusually small doses proved effective in relieving pain: after 75 mg., then 50 mg., daily, to a total of 1-25 g., amelioration persisted for more than a month; then 25 mg. daily proved an effective maintenance dose.

Kenneth Stone.

[This paper has also been published under the title Enervation surrénalienne et polyarthrite chronique évolutives in Rhumatologie, 1951, 3, No. 3, 100, and under the title Les effets de l'enervation surrénalienne sur les polyarthrites chroniques évolutives in Revue du Rhumatisme, 1951, 18, No. 6, 310.]


Scleral rheumatoid nodules were observed to disappear gradually under cortisone therapy. Histological observations portrayed an involution characterized by a large number of vaculated and giant cells. S. J. H. Miller.


The author claims that the parenteral sulphur treatment introduced by him in 1927 for the treatment of syphilis and gonorrhoea has a favourable effect on non-specific rheumatic disorders of the joints, acting on the mesenchymal, and which he calls "Neo-sulfosin". A 0-5 per cent solution of sublimed sulphur dissolved in almond-oil, containing an anaesthetic. It should be administered intraglutely in doses rising from 1 to 10 ml. These injections cause a rise in temperature in the course of 12 hours, but within 1 to 2 days the temperature returns to normal, when a second injection may be administered. A course consists of 6 to 10 injections and may be repeated after an interval of 3 weeks. When a patient's temperature was high a course of neo-sulfosin brought it down (paradoxical effect) and the pains in the joints were considerably reduced.

While the effect on heart-action, pulse-rate, respiration, and blood pressure of neo-sulfosin corresponds to the temporary increase of temperature, normal conditions are restored in ratio with the "stress-like" effect of the injections. The increase in leucocytes is remarkable, 40,000 to 50,000 having been found; this phenomenon is characteristic for all biological immunization reactions. The
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erythrocyte sedimentation rate rises considerably 1 to 1 1/2 hours after injections and remains high during the following 3 to 4 weeks. The author, however, believes that the effect of sulphur treatment does not rest only on pyrexia and the biological phenomena connected with it, but with the effect due to sulphur being "a substance reacting chemically with avidity".

E. S. Fountain.


The authors describe, with some interesting observations, the treatment with cortisone of a single case of rheumatoid arthritis of the infantile or Still's disease group.

The patient, a girl [presumably European] aged 8 1/2 years, had a history of rheumatic joint manifestations for 5 years, with occasional attacks of asthma following infantile eczema. She was confined to bed with much functional disability, fixation of the neck, contractures of the wrist, and subcutaneous nodules at the elbows. The tip of the spleen was palpable, but there was no enlargement of lymph nodes. Radiological examination correlated with the clinical diagnosis of Still's disease.

After a control observation period of 14 days, cortisone was given by intramuscular injection: 150 mg. on the first day, then 100 mg. for 2 days, followed by 50 mg. daily; on the 9th, 10th, and 11th days the dose was increased to 75 mg. daily. A typical satisfactory response occurred, although this was considered to be somewhat delayed. In addition to the usual reversal of the disease process, subcutaneous nodules disappeared and the spleen became impalpable. Improvement was maintained over a period of 2 months by 50 mg. 3 times a week, but not by 25 mg. 3 times a week. Apart from the development of "moon-face" no side-reactions were observed.

Despite maintenance therapy, two relapses occurred, in one of which pyrexia, enlargement of the heart, and pericarditis developed. This was completely relieved by increasing the dose to 100 mg. daily for 5 days together with the administration of salicylates. Numerous laboratory records were recorded. The child was apprehensive and resistant to treatment, which caused pain, and consistently refused to take the drug by mouth because of its taste. The authors conclude that treatment produced temporary symptomatic relief without cure, and that the maintenance dose did not prevent relapses or the occurrence of pericarditis.

Harry Coke.


The authors, working in the New York Polyclinic Post-Graduate Medical School and Hospital, report the effects of pregnenolone acetate and acetoxypregnenolone on fifty patients suffering from various types of rheumatic disease. In six patients with advanced or moderately advanced rheumatoid arthritis, no beneficial effect was observed from administration of 300-400 mg. pregnenolone intramuscularly daily for 18-21 days. Thirty-six cases of bursitis affecting either the subacromial or olecranon bursa were treated with pregnenolone acetate 300 mg. daily. Of fifteen acute cases without calcification, twelve improved after a few daily injections, and three showed no improvement. Of eight acute cases with calcification, six improved after a few injections, and two were unaffected. A few cases of osteo-arthritis were improved by pregnenolone therapy and the authors consider this improvement to be due to an effect on associated soft tissue lesions. The chief disadvantage of intramuscular pregnenolone therapy was local pain at the injection site. Two patients developed sterile abscesses. The authors conclude that pregnenolone therapy was beneficial in certain cases of soft tissue rheumatism.

[Unfortunately the authors do not describe any control cases, and it is in consequence difficult to decide to what extent the good results are due to pregnenolone therapy.]

B. E. W. Mace.


Treatment of Rheumatoid Arthritis with X Rays. (Léčení deformativních arthritid a arthros roentgenem.) FELLER, A. (1951). Lék. Listy, 6, 582. 1 fig, 30 refs.


*(Osteo-Arthritis)*


The authors have employed three types of operation in their series of 236 cases of cup arthroplasty of the hip: (1) the Smith Petersen operation in cases in which the acetabular lesion was severe, but head and neck of the femur could be sufficiently preserved; (2) Judet's operation in cases with a healthy acetabulum and defective head; (3) acrylic arthroplasty, a combination of the two previous methods, in cases in which both the acetabulum and femoral head were diseased.

The patients were operated on at the end of a month. Weight-bearing, where the acetabulum had been reamed out, was not permitted for 4 to 5 months.

Shock was avoided by good surgical and anaesthetic technique. Thrombosis was the worst risk encountered, and occurred in 25 cases with two deaths. There were nine cases of superficial post-operative infection and three of severe infection demanding removal of the prosthesis. There were 22 post-operative dislocations. In five cases there was excessive new bone formation around the hip and in two this was removed with success.

In two cases fracture of the prosthesis occurred and it was replaced.

Results were assessed on a points system based on post- and post-operative examination, and graded from 1 to 6 for pain, mobility, and gait. The results were the most satisfactory and most constant in fractures of the femoral neck. Necrosis of the head with a good neck and healthy hip seen at an early stage gave uniformly good results after Judet's operation.

After cup arthroplasty in cases of arthritis of the hip, two-thirds of the patients were almost free from pain and could flex the hip sufficiently to put on shoes and walk reasonably well. Only a third of the patients required a stick. After acrylic arthroplasty the results in four-fifths of the cases were similar to those in cup arthroplasty. There was slightly more improvement in mobility than with cup arthroplasty, although the improvement in gait was much the same. The functional result was not influenced as much as one would have thought by the pre-operative condition. Only in cases of severe disability in walking did arthroplasty provide amelioration. Preventive and early arthroplasty are therefore not advised.

In infective arthritis of the hip the results were satisfactory where infection had not recurred; there was a grave risk of lighting up an old infection, and the operation should be limited to bilateral cases or those with severe deformity.

In congenital dislocation of the hip the results were most encouraging and are to be reviewed in a subsequent paper.

*J. G. Bonnin.*


Skeletal changes were examined in seven patients with generalized hypertrophic osteo-arthritis, six having severe pulmonary disease and the seventh congenital heart disease. Subperiosteal new bone formation occurred in the long bones, beginning in the distal third of the bones of the forearm and leg. Joints showed chronic inflammatory changes in the synovia associated with degenerative changes in the articular cartilage. Clubbing of the digits was caused by soft-tissue changes, the predominant features being hyperaemia, oedema, increased amounts of loose-textured connective tissue, and mild chronic inflammation.

Theories of the aetiology of the condition are discussed, but no new views are advanced. *R. H. Hepinstall.*

*(Spondylitis)*


A review is given of 160 cases of ankylosing spondylitis treated by the author over a period of 7 years. The technique involved irradiation of the sacro-iliac joints and whole spine, irrespective of the stage of the disease. A skin dose of 2,000r in 4 weeks was given to each section with X-rays at 250 kv, 1 mm Al filtration (H.V.L. 1-9 mm. Cu). This technique led to immediate symptomatic improvement of varying degree in 96 per cent. of cases and to freedom from recurrence of

After reviewing the literature the authors discuss the results of clinical and radiological examination in ninety cases of well-marked rheumatoid spondylitis.

Radiological changes consisted of irregular lytic defects with a punched-out appearance, irregular zones of increased bone density, and "whiskering" or "fringing" of the periphery of the bone. Clinically, there was sometimes pain and frequently tenderness over the site. Changes in the pelvic bones occurred in 74.4 per cent. of cases. The severity of the lesions corresponded to the extent of the spondylitis as a rule, but it was an early feature of the disease in a minority of cases. The commonest site was the ischial tuberosity, but the pubic symphyses and iliac crests were also often involved. Extrapelvic osteopathy occurred in eighteen of ninety cases, the sites being the femur, humeral head, acromion, carpal bones, sternol notch, angles of the scapulae, elbow, lower ends of the tibia and fibula, toes, and a patella. In 22.2 per cent. of cases there was no demonstrable pelvic or extrapelvic osteopathy, despite characteristic sacro-iliac and apophyseal joint changes.

It is concluded that the radiological changes are similar to those found in rheumatoid arthritis and the evidence suggests inflammatory rather than adaptive change.

Kathleen M. Lawther.


This is a report of one Chinese patient who attended hospital at the age of 26 with iritis of the left eye. This was his eighth attack, the first having occurred when he was 9 years old. From the age of 16, he had had intermittent pain in the right shoulder and knee, and when he was 20 years old, the spine became very painful and then bent forward; 2 years later the hips became ankylosed and there was no further pain. His mother suffered from "rheumatism".

He had a gross kyphoscoliosis and ankylosis of both hip joints, and radiographic examination confirmed the diagnosis of ankylosing spondylitis. Examination of the left eye showed marked ciliary congestion and haziness of the cornea, without definite keratic precipitation.

Under treatment the eye rapidly recovered.

The authors point out the similarity of the blood-aqueous barrier of the ciliary body to the blood-synovial fluid barrier in the synovial membrane. They suggest that iritis may be a pointing sign in ankylosing spondylitis, and that this association may occur more frequently than has been realized.

B. E. W. MacE.


(Miscellaneous)


The report authors his experience in the x-ray treatment of over 900 cases of arthritis, bursitis, and radiculitis in the course of the last 5 years. His results were encouraging, complete permanent relief from pain being obtained in many cases, while in the majority of the remainder there was long-lasting improvement. In this paper he analyses the results in 282 of these cases. He first stresses the social importance of rheumatic conditions, which affect 5 per cent. of the population of the United States, and cites a statement from the U.S. Government survey published in 1936 to the effect that "rheumatism ranks first in prevalence, second in causing chronic disability, second in causing invalidity (permanent disablement), and only fourteenth in causing death."

He then reviews the treatment of these conditions by cortisone, ACTH, and prednogenolone, and points to the disadvantages of these preparations. They often have only a temporary effect, and their administration may lead to physiological or psychical disturbances. He briefly touches on gold therapy, and mentions the difficulty of distinguishing the border-line between the therapeutic and the toxic dose.

The radiotherapy of arthritis was first introduced by Sokolov in 1897; although it was not much used in the U.S.A. until 1933, it was extensively employed in Europe. The author quotes the good results obtained with x rays by other workers in cases of spondylitis, especially those of Marie-Strumpell type. He considers early treatment to be essential, and states that the best results were obtained when radiotherapy was combined with breathing and postural exercises. The strength of the current was varied according to the size of the joint to be irradiated, a medium voltage being used for small joints and a high voltage for larger ones. In the acute stage three treatments a week for 2 to 3 weeks were given, followed by one treatment weekly for another 3 to 6 weeks. In chronic cases one or two treatments were given weekly for several weeks. The author found that arthritis of rheumatic origin required a higher voltage and heavier filtration than other conditions.

The most commonly occurring bursitis was that of the...
subdeltoid bursa; bursitis affecting the olecranon or knee and prepatellar bursitis came next in frequency. The author mentions other conditions of the shoulder which may simulate bursitis, and warns that neglected bursitis may lead to ‘‘frozen shoulder.’’ He also refers to brachial neuralgia and points out that this can easily be differentiated from bursitis because in the former, but not in the latter, neuralgia causes pain while the arm is at rest.

Radiotherapy should be continued until complete mobility of the joint is restored; this usually requires eight to ten sessions of 100r each at 180 kVp, with a filter of 0.5 mm. Cu and 1 mm. Al, and a focus-skin distance of 50 cm. Acute and subacute cases responded rapidly; in chronic cases a dose of 1,000r was often necessary to relieve pain and to restore mobility. Improvement was steady though slow.

The author discusses the aetiology of radiculitis, and concludes that this condition may be caused by any disease, toxic action, or mechanical factor which irritates the intraspinal or paraspinal elements. The main feature of radiculitis is pain of typical segmental distribution or arising in areas innervated by the affected nerve root. Involvement of a motor-nerve root results in muscular weakness, atrophy and electrical changes. In brachial-plexus radiculitis, which is often associated with bursitis and arthritis, the author recommends a dose of 1,200r. He also describes the dorsal-spine radiculitis syndrome. The possibility of the co-existence of radiculitis and coronary pain is pointed out. Segmental pain of the abdominal wall, the author states, may stimulate lesions of the gastro-intestinal or genito-urinary system.

In discussing sciatica the author considers only those cases which are due to arthritis. Radiotherapy in these cases proved to be most beneficial. He employed a high-voltage current with 0.5 mm. Cu and 1 mm. Al filtration, an average of 1,500r being given. A 6-inch cone was used to localize the irradiation. In the lumbo-sacral area great care should be exercised in both sexes and a dose of 600r never exceeded. The author considers that in these cases his results were satisfactory.

In giving X-ray treatment for rheumatic conditions great care must be taken of the skin, as it is hypersensitive over affected areas. Any reaction calls for curtailment or postponement of the treatment. A protective ointment containing antihistaminic factor was used with good results.

Seven interesting tables have been included, and these enable results to be appreciated at a glance.

L. G. Capra.


Four patients with recurrent polyarthritis of the rheumatoid type with spontaneous remissions and relapses were found to have intestinal amebiasis which was causing only minor gastro-intestinal symptoms. Anti-amoebic therapy was accompanied by rapid disappearance of the arthritis, which did not recur subsequently.

The authors suggest that the arthritis in these cases was due to sensitization to *Entamoeba histolytica* or its by-products.

A. Gordon Beckett.


In this report from Liege of 100 arthrograms of the knee-joint, the anatomy of the normal joint, and the pathology of traumatic and degenerative lesions of the menisci, crossed ligaments, synovial cysts, and other pathological conditions, with their symptoms, are discussed at length.

In some cases posteroanterior arthrography was often adequate; better results were obtained with a double-contrast method combining the injection of air and from 5 to 20 ml. of a 50 per cent. solution of “umbradil.” The mixing of the injects was ensured by passive or active movements of the joint. The best position for photography was determined by screening, and it is claimed the pictures were clear and well defined. As umbradil is excreted by the body almost entirely within an hour after injection, re-injection was sometimes necessary.

Apart from some intra-articular heat and one case of inflammation of the synovial sac, there were no untoward reactions. The number of cases examined was not considered sufficient to warrant any statistical conclusions.

There are 26 pages of reproductions of radiographs of the joint.

Geo. Vilvandré.


In a description of the pathological anatomy of spondylolistheses [the clearest yet published] the following are among the more important points mentioned. Most cases are bilateral and the fifth lumbar is the vertebra affected in 92 per cent. of cases (the fourth in 8 per cent.). The defect lies between the anterior fragment which consists of body, pedicles, transverse processes, and superior facets, and the posterior fragment consisting of laminae, spinous process, and inferior facets. The defect is filled with fibrous tissue. When the defect is present without forward slipping of the body the condition is called “spondylolisthesis” (symptomless and present in 5 per cent. of all spines), and when slipping occurs the condition is called “spondylolisthesis” (almost always associated with symptoms). Dislocation of the articular facets may occasionally be responsible for spondylolisthesis.

In discussing the causation of symptoms, the author states that trauma is often the final factor which determines the onset of symptoms, hyperextension being the commonest type of injury.

Clinically, pain and deformity are dependent upon, and roughly proportionate to, the amount of displacement. The pain experienced is of two types: lumbo-sacral pain, which is due to the instability, and root pain, due to involvement of the sacral plexus (occurring in 36 per cent. of cases).

The characteristic deformity includes:

1. step-like break in alignment of the tips of the spines;
2. rotation of the pelvis with an elevation of the anterior superior spine in relation to the posterior superior spine;
3. shortening of the trunk, which is noticeable in severe cases;
4. increased upper lumbar lordosis;
5. folds in the loins.

G. H. A. Gordon.
Lateral radiographs demonstrate the lesion and the amount of slipping, but oblique views are valuable in demonstrating the defect.

Treatment is by fixation. Internal fixation by special grafting methods is indicated in the young, but for the older age group external fixation by spinal brace is preferable. Operative treatment is difficult and requires meticulous care in technique, more so than with spinal fusion for other causes. The fusion must be massive; fixation to the sacrum must be secure, as must also be the fixation to one body above the lesion. The technique must give immediate stability, and adequate post-operative protection is necessary for 4 months. Resumption of strenuous activity should be gradual. Two tibial grafts are countersunk into the sacrum and, if necessary, fixed with wire; they are firmly fixed above by wire sutures. These grafts are augmented by cancellous bone. The Stryker frame is used post-operatively. A method is described for correcting the displacement by skeletal traction through the femoral condyles and wings of the ilia. Of 67 patients treated by operation, 56 were cured of symptoms. The most frequent cause of an unsatisfactory result was failure to obtain bony fusion, and most failures were attributed to faulty operative technique. Persistence of severe deformity was responsible for a small group of failures. Thrombophlebitis occurred in five cases, none of which was fatal. Stress fracture of the tibia occurred frequently, but did not affect the final result.

(This Hunterian lecture is likely to become a classic. It is an excellent article in every way. The illustrations are good and the description of operative technique invaluable to the orthopaedic surgeon who has to deal with this troublesome condition.)

L. W. Plewes.


In the author's view the conservative treatment of prolapsed disk should be considered from the mechanical angle. By fixing the spine the swelling is diminished and it is possible for the prolapse to become replaced. If this does occur, then it forms a cicatrix during the rest period and leads to healing. In early and simple cases this may be the only necessary plaster, a plastered bed. Generally this is used only in severe sciatica. The following criteria should be fulfilled:

(a) It is important that there should be rigidity of the lumbar spine with a sclerosis and a positive Lasègue. In most of these cases pain is aggravated on coughing and sneezing, and it is not usual to find any neurological signs, though these may occur.

(b) Simple lumbago may be the first manifestation of a prolapsed lumbar disk. After a certain period the pain diminishes by rest in bed with a board and mattress. No plaster is necessary in such cases. On the other hand, if the lumbago is complicated by sciatica with intense pain which has lasted for some time, then at the first consultation a plaster cast should be applied.


Four cases of intractable pain in the distribution of the brachial plexus are curetted where, from clinical and radiological evidence, a diagnosis was made of congestion of a posterior nerve root by a laterally placed cervical herniated nucleus pulposus. In one case the diagnosis was confirmed by myelography and in another both by myelography and exploratory laminectomy. Division
of the anterior scalenus muscle immediately relieved the pain in all four cases.

[This is an interesting and important paper.] G. F. Rowbotham.


By increasing the distance between the part of the body examined and the x-ray film it is possible to produce an enlarged radiographic image. Under certain technical conditions such an enlarged image may show minute anatomical changes which it would not have been possible to obtain by means of the ordinary radiographic technique. One of the most important conditions for the success of the method is the use of a rotating anode tube with a focus not larger than 0.3 mm. [For details of the technique the reader is referred to a previous publication by van der Plats, but no precise reference to the publication is given.] A. Orley.

Vertebral Retroposition (Reversed Spondylolisthesis).


The author examined a series of 493 cases in which the presence of lumbosacral disk protrusion was confirmed. Of these, 15.6 per cent. showed true retroposition of L 5 over S 1; 35 of the patients with retroposition were examined in more detail. The average backward displacement ranged from 0.3 to 0.9 cm.; in 71.4 per cent. the body of L 5 was slightly larger than that of the 1st sacral segment. In the normal spine this inequality does not disturb the continuous curved outline of the posterior vertebral alignment and therefore does not account for retroposition. It was found that the retroposition was greater than this difference in size in 19.4 per cent. of the cases.

The question of a false retroposition being produced by faulty tube positioning was investigated, and it was concluded that the degree of retroposition could be exaggerated or reduced by this means, but not eliminated. Rotation obliquely may produce an apparent displacement. Flexion or extension did not appreciably affect the degree of displacement. In 85.7 per cent. of the cases antero-posterior facets were found (8.6 per cent. had the internal-external type and 5.7 per cent. were mixed), in 85.7 per cent. the intervertebral space was reduced.

The case of a boy aged 4 years is cited in favour of a congenital aetiology associated with an acute lumbo-sacral angle. The incidence of lombo-sacral anomalies was not found to be greater in the retroposition series than in a control group. The author states that retroposition may occur with

1. disk protrusion;
2. disk degeneration in association with spinal arthritis;
3. rheumatoid spondylitis;
4. infection;
5. trauma.

He does not regard it as a cause of backache, but a radiological indication of disk changes.

John H. L. Conway-Hughes.


Four cases of osteochondrodystrophia deformans (Morquio’s disease) are described. Two of the cases are of pure African native stock, but the others are of mixed African and coloured stock. These appear to be the first reported cases occurring in persons not of pure European racial origin. Consanguinity of the parents is present in three cases. The blood chemistry investigations show no significant departure from normal. A close relationship exists between the many different varieties of dyschondroplasia.—[Authors’ summary.]


To the dozen or so cases of Kast’s syndrome on record the author adds another, in a woman aged 24 years. Both hands showed extensive chondromatosus swellings from the age of 6 onwards. Somewhat later coxa vara and outward convex curves of the upper third of the femur were discovered, while multiple small angiomata developed in the umbilical scar. There is a good reproduction of a radiograph of a symmetrical deformity of tibia and fibula which differs from deformities seen in other systemic affections of the skeleton, but resembles the dyschondroplomatic picture fairly closely.

I. Michielis.


A discussion on the association of ocular and rheumatic disease. Cortisone is probably effective in both by blocking the inflammatory response of collagen tissue to noxious agents.

S. J. H. Miller.


A description of the syndrome with a case report.

S. J. H. Miller.

Gout


Peripheral blood flow was measured by venous occlusion plethysmography in the feet of a man with bilateral podagra and obliterator vascular disease of the legs. During an acute gouty attack the resting blood flow in one foot was increased to 5 ml per 100 ml of limb volume per minute (normal 0-5 to 2-0 ml.), and increased further after a reactive-hyperaemia test. After subsidence of the acute attack the resting flow fell to normal, but again showed a reactive-hyperaemia response. In the contralateral foot the resting blood flow was at the upper limit of normal both during and after a gouty attack; it was not increased after the arterial occlusion test. The obliterator arteritis was most severe in this limb.
The author argues that these observations support the theory of a vasomotor disturbance with local production of a powerful vasodilator as the basis of the acute gouty attack. Ellis Dresner.


Mice weighing from 20 to 32 g. were given subcutaneous injections of 12 μg. colchicine on 3 or 4 consecutive days. This dosage produced within a day or two a high leucocyte count (in some animals of more than 100,000 cells per c.mm.) without a preceding leucopenia. The blood picture showed a shift to the left, with some normoblasts in the myeloid series.

In the bone marrow there was a decrease in granulocytes, but no structural damage such as is seen after bigger doses of the drug. The liver showed interstitial cell infiltration with numerous granulocytes, and extensive parenchymatous degeneration and coagulation necrosis.

H. Lehmann.


"Benemid" is a substance having effects on the kidney similar to carcinamide. The two subjects investigated had an intravenous injection of 25 to 50 mg. of 15N-labelled uric acid and excretion was followed by the isotope dilution method. After several days 2 g. of Benemid daily for 3 days and then more labelled uric acid was injected.

In the non-gouty subject the initial uric-acid pool was 964 mg. and the turnover rate 0.66 pool per day. After benemid therapy the pool size dropped to 466 mg. and the turnover rate rose to 2.4 pools per day. This result is consistent with the view that Benemid inhibits the re-absorption of uric acid. There was a fall in serum uric acid level and a rise in urinary excretion. Similarly, in the subject with gouty arthritis initial pool size was 2,205 mg. and turnover rate 0.48 pool per day. After Benemid the pool size fell to 1,622 mg. and the turnover rate rose to 1.0 pool per day. There was a marked fall in serum uric-acid level, and more uric acid was excreted than could be accounted for by the observed diminution in pool size. Benemid in both subjects was a potent uricosuric agent. It acts probably by blocking uric-acid reabsorption in the tubules.

C. L. Cope.


Non-Articular Rheumatism


Reflex neurovascular dystrophy of the upper extremity may be due to many different causes. It has been reported as occurring in as many as 10 to 20 per cent. of cases of myocardial infarction. It is characterized by painful shoulder disability with stiffness, swelling, and pain in the fingers and hand. After 3 to 6 months there may be disappearance of shoulder pain and hand swelling, but stiffness and flexion deformity of the fingers increase and there may be atrophy of the hand muscles and subcutaneous tissues. Later, trophic changes in the hand are prominent, with contractures, osteoporosis, and subluxations. The technique of stellate-ganglion block is described in detail, and three cases are reported to illustrate the complete success of this form of treatment.

T. Semple.


This is a report of 560 patients operated upon during the last 12 years for prolapse of an intervertebral disk. Except for the last one hundred cases all the operations were carried out by 34 different neurosurgeons from Paris hospitals.

Until 1946 laminectomy was the method of choice, but since then the interlaminar approach, more recently with careful protection of the insertions of the deep back muscles, has been used. Results have improved for three main reasons: (1) better diagnosis; (2) improved operative method; (3) the greater continuous experience of one single surgeon. Additional bone-grafting is only rarely resorted to, while extradural cutting of a nerve root (L 5 or S 1) is favoured in certain cases. [Diagnostic appraisal, surgical procedure, selection of patients, and end-results do not seem to differ much from those of other statistics.]

From middle age onwards a disk which has for long caused lumbar pain may protrude into a joint, and this occurrence is indicated by the appearance of additional sciatic pain. In such cases the surgeon should warn the patient that he will lose only his sacral pain but not his lumbar.

[This is a clearly written article, but a minor criticism is necessary: once more percentages are used for the statistical assessment of small numbers.] L. Michaelis.


Outbreaks of Bornholm disease have been described from time to time in this country since the publication by Pickles in 1933 of his original observations in Yorkshire. Findlay and Howard (Brit. med. J., 1950, 1, 1233) discussed the possible association between this disease and the Coxsackie group of viruses.

The present paper describes a group of six patients with a clinical history approximating to that of Bornholm disease. Of the first five cases the Coxsackie virus was isolated in one, while in the other four a rising agglutination titre was found. No such confirmation was obtained in the sixth case.

[In some previously reported cases of Bornholm disease certain similarities between the symptomatology of epidemic myalgia and polyomyelitis have been described. There is, of course, no reason, from an epidemiological point of view, why patients should not harbour both polyomyelitis and Coxsackie viruses at the same time, but it has been pointed out that their biological behaviour is surprisingly similar. This paper tend to confirm.

The author reviews the history of the isolation of the Coxsackie viruses and their association with the virus of acute poliomyelitis. The evidence put forward by various workers in favour of the theory that epidemic myalgia is caused by one of these viruses is considered. In particular he reviews in some detail the work of Findlay in Great Britain on the detection of complement-fixing antibodies developing in accidental and experimental infections with Coxsackie virus No. 2 which caused symptoms suggestive of epidemic myalgia. The technique of the complement-fixation reaction is described.

The author has studied in great detail an outbreak of epidemic myalgia at Ypres, and has had the sera of 24 patients examined by Findlay for complement-fixing antibodies. It was found that the patients with acute symptoms gave a positive reaction, whereas the sera from patients with a milder form of the disease were negative. In the discussion he describes the various forms which the disease may take and lists the frequency of various symptoms in 81 cases. He finds that the cases tend to fall into two groups—those with the features of epidemic myalgia and those more suggestive of intercostal neuralgia. Some patients showed signs of meningal involvement, such as a positive Kernig sign or increased reflexes. He points out that the disease may simulate other conditions, such as perforated ulcer, peritonitis, or even a myocardial infarct, but he considers diaphragmatic spasm an important sign. The pain is also usually made worse by breathing, laughing, and movements of the trunk. Muscle rigidity is segmental in distribution. The only pleural complications he has seen have been in old cases of tuberculosis.

With regard to treatment, antibiotics had no effect, but sulphanilamide appeared to be of some value, with barbiturates and bromides in severe cases.

R. F. Jennison.


The authors have produced nodular changes in the soft tissues by injecting one group of guinea-pigs with heterologous serum (using normal horse serum) and injecting another group with deoxycorticosterone acetate; they examined these nodules histologically. The histological changes in the group treated with deoxycorticosterone acetate showed big alterations in the subcutaneous connective tissue in the form of oedema, marked congestion of blood vessels, small haemorrhagic extravasations, diffuse infiltration with eosinophilic cells of the type described by Selye as "great, round cells with small dense nucleus in the interior of the granulomatous area". There were less marked changes in the muscular connective tissue and in the subcutaneous periarticular tissue showing oedema, congestion, haemorrhages, and foci of histiocyctic conglomerate in perivascular regions. Oedema and vasal congestion of medium intensity were noted in the synovial membranes as well. The muscular tissue showed limited areas of oedema, areas of degeneration, and fibroblastic proliferation of nodular aspect. All tissues were infiltrated with eosinophilic elements.

In the guinea-pigs subjected to injections of horse serum most marked changes were seen in the skin, often of necrotic-ulcerative type (Arthus phenomenon). This group showed the same characteristic eosinophilic infiltrations.

The histological examination of a subcutaneous nodule removed from a man suffering from fibrositis showed fibrous tissue richly vascularized and congested. The vasal walls were thickened and in their periphery there were agglomerated round cells with deeply-stained nuclei. The connective tissue was oedematous and was infiltrated with fibroblasts, a few scattered neutrophils, and eosinophils. One subcutaneous nodule, removed from a child suffering from rheumatic carditis, showed connective-tissue proliferation with many fibroblasts and giant cells with many nuclei. There was swelling caused by coagulated plasma, often with fibrinoid necrosis. The oedema was most marked in the neighbourhood of blood vessels, which showed congestion and eosinophilic infiltration.

The authors stress the uniformity of the histological changes: vasal congestion, oedema of the collagen tissue, cellular infiltration chiefly with eosinophils and histiocyctic proliferation with fibroblasts, focal distribution in the vicinity of the vessels, and the possibility of reproduction by sensitization.

Fibrositis is considered to be an atypical variety of rheumatoid arthritis and to belong to the group of collagen diseases.

J. Mester.


General Pathology


The mucopolysaccharides of skin, heart valves, aorta, tendon, synovial fluid, and umbilical cord were extracted with 0·33 to 0·5 N NaOH at 0°C. The extracts were neutralized with acetic acid and the protein was removed by treatment with amyl alcohol-chloroform, adsorption on Lloyd's reagent, or zinc hydroxide. Glycogen was destroyed by digestion with amylase. The polysaccharides were precipitated from calcium-acetate-acetic-acid solution by alcohol at 0°C. Five mucopolysaccharides can be distinguished:

1. hyaluronic acid, which is sulphate-free, has a specific rotation of 70° to 80°, and is rapidly digested by testicular and pneumococcal hyaluronidase;
2. chondroitin sulphate A, which is found only in hyaline cartilage, has a specific rotation of 30°, and is hydrolysed by testicular but not by pneumococcal hyaluronidase;
3. chondroitin sulphate B, which has the same...
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composition as A, but a specific rotation of $-50^\circ$, and is resistant to both types of hyaluronidase;

(4) chondroitin sulphate C, which has the same composition as A, but a specific rotation of $-20^\circ$, and is hydrolysed more rapidly by testicular hyaluronidase;

(5) hyaluronidase, obtained only from the cornea, with a specific rotation of $-56^\circ$, is hydrolysed by both types of hyaluronidase. Its amino sugar is d-gluco-
samine, in contrast to the chondroitin sulphates, which contain d-galactosamine.

It is possible to divide tissues into various groups according to their mucopolysaccharide content. Thus vitreous humour, synovial fluid, and peritoneal fluid from a patient with mesothelioma contained only hyaluronic acid. No hyaluronic acid was found in heart valves, aorta, or (probably) tendon. Skin and umbilical cord contained hyaluronic acid together with only one sulphate ester. R. Barer.

Chemical Constituents of Skeletal Muscle from Normal Subjects and Patients with Rheumatic and Non-
2 figs, 14 refs.

Samples of muscle from thirteen healthy adult males and 27 patients with rheumatoid arthritis, gout, tuberculous spondylitis, and other diseases, were analysed for total protein, non-protein nitrogen, collagen, myosin, adenosinetriphosphatase activity, and water, correlation being made with parallel histological study. Methods are fully detailed and results are given as mean values plus and minus standard deviation for each group. No fat extraction was done.

Of the normal subjects there were some who showed lymphocytic infiltration histologically and a significantly smaller amount of myosin. The myosin fraction was reduced in all categories of patients except those with degenerative joint disease. Collagen, surprisingly, showed little variation from the normal range. In the group in which there was greater atrophy histologically (increase in sarclemmal nuclei and diminution of mean fibre diameter) the collagen fraction of the total protein was not significantly altered, although there was marked decrease in myosin. Adenosinetriphosphatase activity was decreased significantly in the group of 27 patients. E. G. L. Bywaters.


A total of 194 cases of synovial sarcoma have been collected from the literature, and to these are added 22 cases from the Mayo Clinic. The tumour appears macroscopically as a greyish-pink mass, often showing definite synovial attachment at one point. The consistency varies; there are often firm areas interspersed with gelatinous and at times haemorrhagic patches. There may be small spaces filled with a stringy yellow fluid. Microscopically there are tissue spaces with a cuboidal or endothelial lining; cell tufts may be present, varying from the compact groups of oval or polygonal cells to villous projections into glandular spaces; there is a varying fibrosarcomatous ground substance. The clinical history is often long, the tumour often being associated with a joint in a lower limb. Local excision is frequently followed by recurrence and finally by general metastasis. Only one patient of the Mayo Clinic series has survived more than 5 years after operation without recurrence or metastasis. Peter Ring.


Fibrinoid and Hydroxyproline of the Rheumatoid Sub-


ACTH, Cortisone, and Other Steroids


Previous work on the association of convulsions with lupus erythematosus has led to the view that the occurrence of epilepsy with rheumatoid arthritis may often indicate the existence of systemic lupus erythematosus. Convulsions were noted in 22 of 144 cases of lupus erythematosus described in the literature, the seizures being terminal in fifteen, and in seven of the authors' series of 28 consecutive patients with a positive reaction to the plasma L.E. test. In two of these seven the convulsions preceded the development of typical symptoms by 2 and 16 years respectively. In three further cases without convulsions there was evidence of cerebral dysrhythmia or histopathological changes. The frequency of convulsions bore some relation to disease activity, their occurrence in some cases being associated with exacerbation. Cortisone or ACTH diminished or abolished the convulsions in some cases; "dilantin" (phenytoinum sodium), which was given to five patients, was without effect.

Abnormal patterns in the electroencephalogram (EEG) were observed in seven of eleven consecutive patients with active lupus erythematosus, including all the five patients with convulsions and two of six in whom there were no convulsions or other cerebral manifestations. Two types of electrical change were noted, the common feature being a slow, diffuse delta activity unequal on the two sides, contrasting with the symmetrical slow, diffuse waves found in idiopathic convulsive conditions. The degree of EEG abnormality tended to fluctuate with the clinical state.

The histological changes seen in the brain varied considerably and none could be regarded as specific. R. Crawford.
Changes in the Bone Marrow in Rheumatoid Arthritis; Effect of Cortisone. (Über die Beteiligung des Knochenmarkes bei der Polyarthritis chronica rheumatica und ihre Beeinflussung durch Cortison.)


During the last 10 years eighty patients with rheumatoid arthritis have been investigated, six of them having been treated by short courses of comparatively small doses of cortisone. Chronic granulocytopenia was present in five cases and in one of them an anaemia. Bone-marrow biopsy showed maturation arrest at the metamyelocyte and stab-cell stages; this was not influenced by cortisone. The functional activity of leucocytes was investigated by studying the disposal of bacterial substances, using a preparation made from Bacterium coli; this was diminished throughout. In five cases in which the leucopenia was not so severe and in five with anaemia, bone-marrow changes were similar. In another case thrombocytopenia persisted for 2 months. Of the four patients with increases in the blood from 12 to 13 days after a given cortisone. In most cases the proportion of plasma cells in the marrow was less than 2 per cent., but in one it was 3-4 per cent. [This is much less than found by Hayhoe and Robertson Smith, J. clin. Path., 1951, 4, 47.] All the sixteen cases in which there was evidence of bone-marrow damage showed reactions to the injection of bacterial products similar to those seen in marrow hypoplasia or aplastic anaemia. E. Neumark.


The authors describe their experience with the intravenous administration of ACTH in 100 subjects. The investigation was carried out at the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School. ACTH was dissolved in 500 ml. saline solution or 5 per cent. dextrose solution and infused intravenously over a period of 8 hours. The fall in circulating eosinophils was regarded as a qualitative measure of adrenal response, and the rise in urinary 17-ketosteroids as a quantitative measure. It was found that an 8-hour intravenous administration of ACTH stimulated the adrenal cortex for 16 to 24 hours, thus approximately meeting the patient's requirements for the day. When 20 mg. ACTH was given daily to a subject with normal adrenal glands, a maximum response was attained in from 3 to 8 days. With the dose of 10-20 mg. Larger doses did not appear to increase adrenal cortical activation any further once this maximum was reached. The effect of 20 mg. ACTH given intravenously over a period of 8 hours was comparable to that obtained from an intramuscular injection of 5 to 10 times this dose when injected 6-hourly in 24 hours.

No anaphylactoid reactions were noted in over 100 patients or normal subjects, many of whom had received repeated infusions. The authors advise, however, that until a larger group has been studied patients should be watched for the first 30 minutes of the infusion for any evidence of anaphylaxis. No evidence was found of a diminished response to ACTH with repeated administration. Intravenously administered ACTH resulted in a normal adrenal response in four patients who had become unresponsive to the same preparation of ACTH injected intramuscularly.

The authors describe cases of rheumatoid arthritis, psoriasis, and exfoliative dermatitis which illustrate the effectiveness of intravenously administered ACTH in one-fifth to one-tenth of the dosage usually required by the intramuscular route. C. E. Quin.

Sustained Pituitary Adrenocorticotropic Hormone (ACTH).


Twenty-four rheumatoid arthritis patients were given daily intramuscular injections of pituitary adrenocorticotropic hormone (ACTH) suspended in 5 ml. of a sustaining menstruum consisting of 18 per cent. non-antigenic gelatin made hypertonic with 8 per cent. dextrose. Serial circulating eosinophile counts showed maximum physiologic effect from a single injection to be reached in from 5 to 12 hours. The effect was well maintained for 12 to 24 hours, gradually diminishing from 24 to 48 hours. As each succeeding daily injection of the hormone was given before the effect of the preceding one was gone, a mild continuous adrenal cortical stimulation was obtained. Adequate clinical response was maintained with approximately 60 per cent. less hormone than was formerly used. Chronically ill patients, in whom pituitary adrenocorticotropic hormone was formerly thought to be contraindicated, responded satisfactorily to this treatment.—[Author's summary.]


This is a study of 21 patients, of whom eighteen had severe chronic rheumatoid arthritis, two ankylosing spondylitis and one gout. Sixteen cases were given pregnenolone intramuscularly in doses of 100-300 mg. Nine of these patients were afterwards given ACTH.

Most of the patients given pregnenolone showed some decrease in discomfort at some stage, but there was no evidence of a sustained action of the drug. One patient felt much better after 2 months' treatment; she later had ACTH with much greater benefit, but relapsed after this was discontinued. With this exception, no patient given pregnenolone or 21-acetoxypregnenolone produced any noticeable improvement in joint function, gain in weight, or reduction in sedimentation rate.

When ACTH was given, rapid clinical recovery occurred during the course of treatment.

Side effects of pregnenolone administration were rare, and usually confined to painful lumps at the site of injection.

The authors have used ACTH as a standard against which the other remedies are measured. On their results, pregnenolone and 21-acetoxypregnenolone are innocuous but have no useful antirheumatic effect.

B. E. W. Mace.

Cortisone in the Treatment of Acute Rheumatic Fever.


The authors report the effect of cortisone on an 8-year-old girl suffering from acute rheumatic fever. The patient had been ill for 17 days. She had been
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of ACTH suggest that after a prolonged period neutralizing antibodies may develop against particular batches of ACTH, and this is possibly the basis of the ACTH-refractory state.

B. E. W. Mace.


This is the case report of a 58-year-old man with rheumatoid arthritis and chronic hepatitis of 1½ years’ duration who was given treatment with ACTH and later cortisone, during which he developed a pulmonary lesion that was eventually found to be tuberculous.

Before treatment was started the patient had a persistent pyrexia for which extensive investigations revealed no cause and which was presumed to be a manifestation of rheumatoid arthritis. A chest radiograph was clear. ACTH was effective in relieving the symptoms and the pyrexia, but after 6 weeks there was an increase in cough and a rise in temperature, and an inflammatory lesion in the right lung field was found on radiological examination. This lesion gradually extended, and 6 weeks later tubercle bacilli were found in the sputum. The patient survived, but has made little progress.

The development of tuberculosis in this patient may possibly have no connexion with the hormone therapy (just before treatment was started he was in the next bed to a tuberculous patient), although this is most likely. The authors point out the increasing evidence that ACTH and cortisone exert much influence on physiological reactions to insult, and suggest that until information is more precise these hormones should be used with extreme caution.

B. E. W. Mace.


Eight patients with rheumatoid arthritis of severe grade received subcutaneous implantations of 900 mg. cortisone in the form of twelve pellets, each of 75 mg. Prompt clinical improvement of moderate degree occurred in all patients and was sustained for 2 to 4 weeks, whereupon all except one relapsed to their pre-treatment condition. It is considered that subcutaneous implantation is a possible means of giving cortisone.

G. M. Findlay.


The authors record their experiences of the treatment of three cases of juvenile rheumatoid arthritis with ACTH. In all cases the clinical state was assessed and the following investigations were carried out: glucose tolerance test; serum potassium, chloride, and protein estimations; uric-acid-creatinine ratio; 17-ketosteroid excretion; erythrocyte sedimentation rate (E.S.R.); and antihyalurondase [type not stated] titres.

The first patient was a girl aged 13 with chronic rheumatoid arthritis. On 500 units ACTH per day there was clinical improvement. As the dose of ACTH was

treated with salicylates, but in spite of this her condition had deteriorated. On admission she was febrile, erythema marginatum was present and there were signs of cardiac failure. There was marked cardiac enlargement clinically and radiologically. An E.C.G. showed changes compatible with acute pericarditis. Blood examination revealed: Hb 63 per cent.; W.B.C. 21,300 per cu. mm.; E.S.R. 115 mm. in first hour.

She was treated with cortisone for 18 days. The temperature began to fall on the third day and was normal on the seventh day. At the same time signs of cardiac failure disappeared. A systolic murmur was present on admission and a mild diastolic murmur developed during cortisone therapy and persisted for three months. Auscultatory findings were confirmed by phonocardiograms. An x-ray revealed a dramatic reduction in heart size to just slightly above normal on the seventh day. Electrocardiograms returned to normal more slowly. The erythrocyte sedimentation rate returned to normal on the fourteenth day.

On improvement after cessation of cortisone the patient was allowed up in a chair, but this caused a rise in temperature and erythrocyte sedimentation rate. In all, four months’ bed rest was necessary before the patient was allowed up.

The authors consider that the rapid clearing of cardiac failure and return to normal cardiac size on the seventh day of treatment suggest that cortisone has a beneficial effect on the damaged myocardium.

C. E. Quin.


In an earlier paper (Brit. med. J., 1950, 2, 1019) was described the treatment of rheumatoid arthritis with small doses of ACTH over a prolonged period. The authors now report further results, but deal mainly with the development of a “refractory state” to ACTH after some weeks’ treatment. ACTH was given to twenty patients for periods of 1½ to 8 months; all of them showed initial improvement but relapse in some degree or another in nineteen either during or after treatment. It was observed that after a variable period of treatment the dose of ACTH which had originally been effective was no longer so, and clinical deterioration occurred.

Attempts were made to establish the cause of these relapses under treatment. It was found that in six patients who no longer responded to ACTH cortisone produced a satisfactory remission, and it is concluded from this that a diminished response to cortisone-like substances in the “target organs” is not the cause of the ACTH-refractory state. Tests of thyroid function with radio-active iodine gave normal results in four patients who had failed to respond to ACTH; this probably excludes “corticogenic hypothyroidism” as a cause of this unresponsiveness to ACTH. cortisone produced the adrenal glands to fail to respond to ACTH after a time could not be dismissed, but this is considered unlikely: the level of 17-ketosteroid excretion and the degree of eosinopenia often bore no relation to the clinical picture. The intravenous administration of ascorbic acid in large doses in an attempt to restore the theoretically depleted adrenal cortical content was without effect. Observations made with different batches and makes
lowered the E.S.R. rose, but the clinical improvement persisted. When ACTH was replaced by saline clinical relapse occurred. An exacerbation of arthritis, 5 months after ACTH had first been given, responded poorly to a fresh course of ACTH, but the authors still thought the patient's condition was much improved by the total ACTH course. A second patient, aged 4, improved on 4 mg. ACTH per day, but showed only a subjective improvement on a daily dose of 2 mg. Decreased sugar tolerance and pigmentation appeared as side-effects with the larger [though still very small] dose. A third patient also showed some improvement. The authors add an interesting study of 17-ketosteroid excretion.

"[It is notoriously difficult to draw conclusions on the treatment of a disease like rheumatoid arthritis which is always liable to undergo spontaneous remissions, and the authors might have done well to let their judgment be tempered with more caution on this score. The statement that ‘one must conclude that in the pathogenesis of rheumatic diseases the adrenal cortex must play a part’ seems unwarranted.] G. Loewi.


The authors report two cases of spontaneous hypoglycaemia which occurred shortly after the cessation of insulin hypoglycaemic therapy which had been given to a series of patients with rheumatoid arthritis. The attacks were controlled by a high-protein diet with a feed at bedtime, and the tendency to them disappeared within 2 weeks.

W. S. C. Copeman.


In this paper is presented the further work which has been done by the authors in an endeavour to stimulate the pituitary-adrenal complex by means of hypoglycaemia. They report marked temporary improvement in 44 per cent. of 72 patients with rheumatoid arthritis who had been subjected to this procedure. Complete clinical remission was obtained in seven cases after 6 months. In a control series of patients on a simple hospital regimen and without hypoglycaemia, only 14 per cent. had marked improvement. A second course of treatment was less successful than the first.

The authors consider that the clinical response to hypoglycaemia can be correlated closely with that evoked by ACTH.

W. S. C. Copeman.


The authors have given ACTH intravenously to 25 patients under treatment in the Veterans' Administration Hospital, Long Beach, California. ACTH was administered each day in one of three ways: by continuous intravenous infusion for 8-20 hours, by intramuscular injection every 6 hours, and by continuous intramuscular drip. The daily dose for intravenous administration varied between 5 and 20 mg. and was dissolved in distilled water containing 5 per cent. glucose and 0-2 per cent. potassium chloride. When given for 20 hours, the ACTH was placed in 1 to 2 litres of fluid; when it was given for 8 to 12 hours, 0-5 to 1 litre was used. Of the 25 patients in this series, twelve had rheumatoid arthritis; three rheumatoid conditions, four bronchial asthma, and one lupus erythematosus, one polyarteritis nodosa, one scleroderma, one rheumatic fever, one neurodermatitis, and one eczematoid dermatitis.

It was found that all patients responded to intravenous administration of 5 to 10 mg. ACTH and many patients could be maintained on doses between 2-5 and 5 mg. daily.

The response to continuous infusion of a single dose was roughly proportional to duration of administration. Thus, in one patient given a constant daily dose of ACTH, the 20-hour infusion was more effective than the 12-hour infusion, and this in turn was more effective than intravenous injections every 6 hours. Continuous intravenous infusion was more effective than 8-20 continuous intramuscular drip. No patient failed to respond to ACTH by the intravenous route and none was refractory to subsequent treatment with this drug. The authors consider that ACTH is effective by the intravenous route in one-tenth to one-twentieth of dosage required for intramuscular administration. The reasons for this difference are discussed, and the authors suggest that the greater effectiveness of intravenous infusion is due to the more continuous adrenal cortical stimulation and to the fact that destruction does not occur at the injection site.

C. E. Quin.


Treatment with cortisone of two cases of polyarteritis nodosa resulted in improvement of subjective symptoms with fall in temperature and lowering of erythrocyte sedimentation rate. Improvement was prompt, but cessation of treatment was followed by partial relapse. Active lesions were demonstrated by biopsy, but at necropsy only healed lesions were found. Death was due to the ischaemic effect of numerous healed lesions. In cases previously described there were widespread healed lesions. The present cases differed from spontaneously healed cases in the rapidity of healing—3 weeks and 3 months respectively.

The treatment caused atrophy of the testes, adrenal glands, and pituitary.

D. M. Pryce.


The authors consider that criteria for judging improvement during drug treatment in rheumatoid arthritis are unsatisfactory. They record studies of the internal temperature of affected joints, suggesting that such measurements may prove more valuable. Previous work had shown the temperature of a rheumatoid arthritic joint varies little from day to day under standard conditions, except when changes in the activity of the
disease occur. To determine the temperature a filamentous copper-constantim thermocouple was inserted into the joint space through the bore of an aspirating needle, an electronic potentiometer automatically recording the temperature readings.

The effect of various anti-rheumatic agents was studied, usually in patients with an affected knee-joint. Throughout the observation period daily temperatures were recorded in 21 patients with active rheumatoid arthritis. Eleven of these received cortisol parenterally (300 mg. on the first day, then 100 mg. daily) and ten patients received ACTH (80 mg. daily). In addition, cortisone acetate tablets were given orally to six patients with rheumatoid arthritis (150 mg. daily for 3 days, then 100 mg. daily), and a further eight patients received various supposedly anti-arthritic steroids.

In all the patients given ACTH or cortisone parenterally a fall in joint temperature from a minimum of 0-7° C. to a maximum of 2-7° C. (mean 1-4° C.), was recorded, within 24 hours. During the pre-injection period there had been a maximum fluctuation of 0-4° C. Joint temperature continued to decrease, and approached normal levels in 3 to 5 days. The fall preceded detectable clinical improvement in fourteen of the 21 patients, and in all but two preceded by some days any significant change in erythrocyte sedimentation rate. In all cases joint temperature began to rise within 24 to 48 hours of cessation of treatment; this rise preceded clinical relapse in seventeen instances. In fourteen patients joint temperature had returned to pre-treatment levels within 1 week of stopping cortisone or ACTH therapy. In all six patients receiving cortisone orally a marked fall in joint temperature was noted within 48 hours. The steroids used were 16-dehydrocortisone acetate, 21-acetoxycortisol, 3β-pregnene-3, 21-dione, and testosterone propionate, and the eight patients who received them believed they were receiving cortisone. None of these patients produced any significant fall in joint temperature, nor was there any clinical improvement. In each case a prompt and marked fall occurred after cortisone.

The authors suggest that serial joint temperature determination might provide a rapid and relatively simple test of drug effectiveness in active rheumatoid arthritis. By this criterion no other drug has been found to have an effect comparable to that of ACTH or cortisone; and it is shown that oral administration of cortisone is comparable in effectiveness with parenteral administration. Kenneth Stone.


The use of cortisone in the treatment of rheumatoid arthritis is beset with problems, including the withdrawal effects and relapse when the hormone is discontinued. For sustained improvement in a chronic disease such as rheumatoid arthritis it appears that cortisone must be given more or less continuously; but uninterrupted administration over long periods is liable to produce unpleasant, and sometimes dangerous, side-effects.

The author has treated sixty patients with rheumatoid arthritis, an electronic potentiometer being used uninterruptedly for 6 to 15 months. Large suppressive doses were used, followed gradually by reduced dosage, and finally by smaller maintenance doses. In this way adequate degrees of therapeutic control were maintained in a majority of cases. The ability to maintain satisfactory improvement varied indirectly, in general, with the severity of the rheumatoid arthritis. In 47 per cent. of severe cases very marked or marked anti-rheumatic response was maintained for long periods. This was so also in 70 per cent. of moderately severe cases and in 92 per cent. of moderate or mild cases. It was found that adverse hormonal side-effects often developed, and were the chief obstacles to better results in the more severe cases in which relatively large maintenance doses were required to support satisfactory improvement. Unwanted side-effects developed also in 40 per cent. of all cases at some time during treatment, although most of these reactions were of a comparatively mild type and disappeared or lessened when the dosage of cortisone was reduced. It was unfortunate, however, that the lower dosage often, as would be expected, resulted in a clinical deterioration in the arthritis.

Prolonged uninterrupted cortisone therapy, evidence of functional suppression of the adrenal cortex was present, as indicated by a decreased response of circulating eosinophils to exogenous ACTH. This depression of function, however, was found to be of a temporary nature, and in patients from whom cortisone was withdrawn after 6 to 14 months of continuous administration clinical function tests returned to normal within periods ranging from 10 to 90 days.

The author points out that as experience with hormone therapy of this type expands, it becomes increasingly evident that there are distinct limitations, difficulties, and dangers in its long-term administration. In the present state of knowledge it appears that cortisone may be employed as a powerful weapon in the management of rheumatoid arthritis in many cases, but it should not be considered as the treatment of choice in most cases, and not as a cure in any case.

[This paper reports the largest and longest series of cases treated with cortisone to date; the author was a pioneer in its clinical development. It is therefore of great importance, and should be read by all clinical workers in this field.] W. S. C. Copeman.


Investigation of the effect of intra-articular cortisone was carried out in five patients. The authors had previously noted that cortisone, while exerting its effect on rheumatoid arthritis or similar conditions, caused no change in joint effusions. ([This is not the experience of other workers.] They now show that the hormone is equally ineffectual in this respect when injected into the joint. Tolerance to the injection was good: there was no increase of pain or swelling, although one joint received a total dose of 225 mg. Cell counts of the effusion fluids showed no consistent changes after injection of cortisone either in total or differential values.

ACTH, in doses of 20 mg., was injected into hyaluraloses in three patients to determine the permeability of the synovial membrane to this substance. A drop in the eosinophil count, comparable with that occurring after subcutaneous injection of the same
quantity into the same subjects, was observed. The ACTH molecule is large, and it is surprising to find that it so readily diffuses through synovial membrane: the explanation may be that the active part is a much smaller molecule.

Insulin was given by the intra-articular route in two patients. Blood sugar estimations showed a lowering of values after the injection, and a rise to the original level or above in 2 to 4 hours. In one case, a subcutaneous injection of the same dose (10 units) produced a comparable fall. In both cases there was a drop in the eosinophil count after injections.  C. E. Quin.


During pregnancy, production of progesterone, as measured by the urinary excretion of pregnanediol, is substantially increased, and in jaundice there is impaired inactivation of progesterone with retention of progesterone metabolites. Pregnancy and jaundice may both benefit rheumatoid arthritis, and this provides the rationale for the use of progesterone in this disease.

Progesterone was given in doses of 200 to 500 mg, daily for periods of 13 to 30 days to eight women with rheumatoid arthritis. In only one case was there substantial improvement, and this was subjective only. Erythrocyte sedimentation rates and the results of other laboratory investigations were unchanged except that the one subject showing marked improvement had a moderate rise in 17-ketosteroid excretion. There were no toxic manifestations from treatment but menstruation was suppressed in all cases. The proportion of progesterone excreted as pregnanediol (measured in five subjects), was 9 to 22 per cent.

The authors conclude that progesterone in large doses produces no consistent benefit in rheumatoid arthritis and that the steroid is not solely responsible for the beneficial effects of pregnancy. [Because of differences in the methods of estimating pregnanediol and in the dosages used, the figures for urinary excretion of pregnanediol cannot be compared with the findings of Somerville and others (Lancet, 1950, 1, 116) that in rheumatoid arthritis there is an abnormally high urinary excretion of parenterally administered progesterone.]  Ellis Dressner.


Earlier clinical observations of the effect of intensive salicylate therapy on the urinary excretion of adrenocortical steroids, and also various independent observations of similar effects in intact rats, led the author to investigate the action of salicylates on hypophysectomized rats, in an attempt to determine the site of action of the drug. Of the 25 male hypophysectomized rats used, four were injected subcutaneously with ACTH to test the response of the adrenal glands, twelve received an injection of sodium salicylate (500 mg. per kg. body weight), and the remaining nine served as controls. The plasma-salicylate level, as estimated by Van Cauwenberge's method, rose to about 51 mg. per 100 ml. (that is, above therapeutic levels in the treatment of rheumatic fever), but no significant decrease was observed in adrenal ascorbic acid, adrenal cholesterol or in circulating eosinophils, indicating that salicylic acid had no effect on the adrenal cortex in absence of the pituitary. The expected cortical response was obtained, however, in those hypophysectomized rats injected with ACTH. The inefficacy of salicylate therapy in patients whose blood-salicylate level is high may be explained by an alteration in the hypothalamus-pituitary-adrenal system, which can be investigated not only by Thorn's test but also by a sodium-salicylate test described by Roskam and others (Lancet, 1951, 2, 375).  Nancy Gough.


The Effect of Acute Stress on "Formalin Arthritis" in the Adrenalectomized Rat treated with Cortisone and/or Deoxycortic. (Effetti di stress acuti sulla così detta "artrite da formalina" nei ratti surrenecotomizzati e trattati con cortisone e/o deossocorticosterone.) PATRINO, V., and MAGLIOCCA, R. (1951). Rif. med., 65, 917. 6 figs, 15 refs.


**ABSTRACTS**


The metabolic effects of giving Compound F, 400 mg. daily by mouth for 4 days, to a healthy volunteer have been studied. Excretion of sodium and of chloride was reduced and oedema developed. Excretion of nitrogen, sulphur, glucose, and uric acid were increased, and output of 17-ketosteroids and of 11-oxosteroids was doubled. Eosinophil cells were absent from the blood. The effects of ACTH administration were closely simulated. The only important difference between the actions of ACTH and of Compound F was in the esterified serum cholesterol levels which was reduced by the former but was not affected by the latter. This difference is understandable if the esterified cholesterol of serum is a precursor of adrenal hormone.


Of four patients with severe essential hypertension, two were given cortisone and two ACTH; in each case the dose was 100 mg. per day. The effect of this treatment on blood pressure, renal function, and some serum levels was studied. The cases were selected because of their known stability of function and blood-pressure level; dietary intake was kept constant and treatment was not started until after an adequate control period. Blood-pressure readings showed no dramatic change. There was a reduction in systolic pressure in one patient receiving cortisone, but this effect could not be repeated by a subsequent course of treatment. The other patients showed no significant change either during or after treatment. An attempt has been made at statistical analysis of the results.

No definite effect on the concentrating power of the kidneys or on the degree of proteinuria was observed during or after treatment; nor were any consistent changes of significance observed in the estimations of renal blood flow, filtration fraction, or tubular secretory capacity for para-aminomurpurate. The tubular secretory capacity for glucose, however, was altered, being increased in one patient having cortisone and somewhat diminished in the other three; it persisted at a low level in them afterwards. Glycosuria appeared in these three patients during treatment and persisted after treatment was stopped; although the blood glucose levels, fasting and 2½ hours after meals, rose during treatment, they did not become abnormally high, and the glycosuria appeared to be due to depression of tubular reabsorption of glucose.

The patients receiving ACTH showed an increase in the excretion of urinary corticoids; no definite change occurred in those receiving cortisone. In all four patients the serum cholesterol level diminished during treatment and rose above the original level after treatment. No other significant changes in serum level were observed.

B. E. W. Mace.


The rate of absorption of hormone pellets implanted subcutaneously has been determined. Pellets were weighed before sterilization and again when removed at varying times after implantation. Correction was made for the "ghost" produced by some types of pellet.

Fused testosterone 100-mg. pellets are absorbed at about 1-1 mg. daily. Compressed tablets are absorbed at the same rate at first, but more irregularly later. Absorption of testosterone propionate 100-mg. pellets, either fused or compressed, is about 0·6 mg. daily for the first 80 days.

Absorption of oestradiol was more irregular and slower, averaging about 0·24 per cent. per day. At 240 days only about 50 per cent. was absorbed. The rate for the propionate was similar. Absorption from a 100-mg. pellet of stilboestrol or of hexoestrol is about 1 mg. daily. Progesterone is too frequently extruded for
satisfactory observations to be made. Fused deoxy-
cortone tablets of 100 mg. absorb at the rate of about
0-4 mg. daily, less than 50 per cent. being absorbed in
220 days. Rate of absorption appears to be well related
to the surface area of the pellets remaining at the time.

C. L. Cope.

An Extra-adrenal Action of Adrenotropic Hormone.
Previous experiments by the author have shown that
stress causes secretion of the thymus during the first
stage of the "alarm" reaction. This can be prevented
by adrenalectomy, but it occurs in the absence of the
adrenal glands if adrenocortical extract is given. In
the present experiment 120 female rats were divided into
four groups and adrenalectomy was performed upon
all of them. One group received hypertensinogen, which
was used as representative of a non-hormonal protein;
one of the other three, one received ACTH alone;
one ACTH together with cortisone, and the other was
given hypertensinogen with cortisone. In none of the
groups did a significant loss of body weight occur.
Neither ACTH nor hypertensinogen produced any
significant involution of the thymus, and cortisone when
given in conjunction with hypertensinogen caused only a
mild degree of thymolysis; but cortisone and ACTH
together caused a significant increase in involution, which
was measured by weighing, and confirmed by histological
examination.

H. Hersheimer.

Effect of ACTH and Cortisone on Certain Immunologic
Mechanisms including Reversed Anaphylaxis. ARBES-
J. Allergy, 22, 340. 13 refs.
Forssman antibodies were prepared and the minimal
amount necessary to produce fatal shock by intracardial
injection determined in normal guinea-pigs. This
amount varied from 0.25 to 1 ml. Later, ACTH was
injected in doses of 0.1 to 20 mg. 8 to 24 hours before
the intracardial injection of Forssman antibodies. Doses
between 0.5 and 2 mg. seemed to give some protection,
but this effect was absent with higher and lower doses.
Cortisone had no effect. In another series of experi-
ments reversed anaphylaxis was produced by the injection
of rabbit antiserum into guinea-pigs. Here thirteen of
the twenty untreated animals died in shock, whereas of
the twenty treated with 6 and 10 mg. ACTH, only six
died. Under cortisone one animal out of twenty died,
compared with eight when untreated. In ordinary
active and passive anaphylaxis no protective effect
of ACTH or cortisone was found. These substances
were also given early during the period of sensitization,
and the absence of any effect shows that they do not prevent
the formation of antibodies. In three ragweed-sensitive
patients who were treated with about 100 mg. ACTH
for one week the reagin titre of the serum did not change.

H. Hersheimer.

Lethal Infection with Coxsackie Virus of Adult Mice given
Cortisone. KILBOURNE, E. D., and HORSFALL, F. L.
The fact that the adult mouse has proved to be
insusceptible to Coxsackie virus infection led the authors
to investigate whether previous injection of cortisone
would affect this insusceptibility. Experiments were
carried out on Rockefeller Institute Swiss mice—both
"suckling" mice (less than 1 day old) and "adult"
mice which were sexually mature, of an average weight
of 6 g., and 3 to 4 weeks old. Two strains of Coxsackie
virus—Conn. No. 5 and RB—were used. Antiserum for
the neutralization test were heated at 56° C. for 30
minutes. Cortisone acetate was injected subcutaneously
in 2-5 to 5 mg. doses; most of the adult mice survived this
dose for at least 8 days, when the experiment was ter-
minal. Pfannstiel peptone broth and 0.85 percent
NaCl buffered to pH 7.2 with phosphate were used for
control injections.
One subcutaneous injection of cortisone was given to
mice 1 to 2 hours before inoculation of the virus. Light
erth anaesthesia was induced when mice were injected
by the intracerebral route. Control groups of mice were
given injections of both cortisone and broth in quantities
and by routes identical with those employed in virus-
infected animals. When the intraperitoneal route
was used the viral suspensions were administered in
amounts approximately proportional to the size of the
mice inoculated (0.05 ml. virus suspension to 1.7 g. body
weight). All viral inocula contained penicillin and
streptomycin and were bacteriologically sterile.
Three days after inoculation all mice given cortisone
and virus were dead, while controls given either virus
or cortisone alone after 8 days. It has been ascer-
tained that in cortisone-injected mice viral multiplication
took place, the lethal effect was serially transmissible,
and multiplication of virus and lethal effect could be
neutralized by specific antiserum. It was found also
that 17-week-old mice weighing 35 g. are sensitive to
the lethal infection if they have previously been given an
injection of 7.5 mg. cortisone. The injection of the
adult mice pretreated with cortisone took place also with
Coxsackie virus which had not previously been passed
through infant mice, but which was derived directly from
a human source (stool).
Intraperitoneal injection proved fatal in 3 days, while
mice receiving virus by the intracerebral route succumbed
more slowly, dying 7 days after inoculation. It should
be pointed out, however, that the intracerebral inocula-
tion was only one-tenth of that given intra-
peritoneally. A 1 in 100 dilution of brain tissue from
mice which had received an intraperitoneal injection of
infected stool promptly killed all animals when passed
with normal mouse serum, but caused no evident disease
or death in the presence of specific immune serum against
the RB strain of virus.
Negative results were obtained from control mice in
all experiments.
Observations on the adult mice pretreated with
cortisone and infected with Coxsackie virus revealed that
2 to 3 days following inoculation some animals became
temporarily hyperexcitable and showed huddling
ruffled fur, arched backs, and laboured respiration with
expansive unrespiratory breathing and lethargy proceeding
to stupor and sudden death.Paralysis, tremor, and
convulsions were not, however, noticed.

J. W. Czekalowski.

Cortical Secretion of the Isolated Perfused Adrenal.
38 refs.
The main object of this investigation was to determine
whether substances other than adrenocorticotrophic
hormone (ACTH) can exert a humoral control on the
ABSTRACTS

adrenal cortex, a tissue which lacks secretory nerves. The investigation was carried out by subjecting the isolated perfused adrenal gland of the dog to the action of substances of physiological interest. Perfusion was completed with a Dale-Schultze pump filled with blood from the same animal. Drugs were either added to the reservoir of the perfusion system or infused straight into the arterial cannula. The adrenal effluent was centrifuged and the plasma assayed for cortical hormone on adrenalectomized rats, the mean survival time at low temperature being used as measure of potency. The concentration of adrenaline in plasma prepared from adrenal effluent was assayed on the rabbit intestine.

Before the administration of the series of drugs, it was shown that the perfused adrenal secretes cortical hormone at a fairly high and steady speed without being supplied with ACTH. The "standard" material for comparison was whole-gland extract, since neither Compound E (Kendall) nor desoxycorticosterone esters have the same effect as whole-gland extract on the survival of adrenalectomized rats kept at low temperature. The slopes of the dose-response curves with the synthetic materials were not the same as that with whole gland extract. When the adrenal cortex of the dog is supplied with ACTH (24 to 54 mg. per 100 ml. blood), there is an immediate increase in hormone production. After withdrawal of ACTH there is little reduction in its secretion for at least 2 hours. A rise in the blood sugar or lactate level did not produce any direct effect on the rate of cortical secretion. Of the other organic substances tested at naturally occurring dose levels, amino-acids, sodium ascorbate, and adrenaline were without effect on the output of hormone in the perfused gland. Adenosine triphosphate and creatine phosphate, however, stimulated the activity of the cortex for a period outlasting the intra-arterial infusion of the compound by about 15 minutes. These compounds are substances with readily available energy and compare with adenosine, adenosine diphosphate and inorganic phosphate, all of which were without effect.

Of the naturally occurring constituents of plasma tested, only inorganic kation proved to be endowed with a direct action on the adrenal cortex. The rate of production of cortical hormone was accelerated by a decrease in the sodium potassium ratio from its normal figure of approximately 45 to 10 or less. This effect is obtained by increasing the potassium without altering the sodium content, but not by reducing plasma sodium even to levels below those observed in adrenalectomized dogs. Of the other compounds tested, nicotine, colchicine, and morphine failed to stimulate secretion in the perfused adrenal. Their in vivo action, therefore, must be due to the release of ACTH. On the other hand, histamine in large doses sometimes stimulated the adrenal cortex, but it is certain that such concentrations of plasma histamine (10 mg. acid phosphate per 100 ml. of plasma) do not normally occur, even in adrenalectomized animals.

G. B. West.


Experiments are described which demonstrate the effect of a daily dose of 10 mg. cortisone on the growth and organization of autografts and the survival time of homografts in the rabbit. Grafts were transplanted from a donor to two rabbits, all three being of wide genetic disparity; at the same time autografts were implanted alternately with these homografts. One of the recipients was acted as control; the other received cortisone from the day after operation. The homografts carried by the cortisone-treated animals survived for about 25 days, while those carried by the controls were destroyed within 10 days. The control animals, being now immunized, were given cortisone and the transplanting was repeated 4 days later. These homografts survived little longer than the previous ones.

It was found that cortisone retarded the development of granulation tissue in the graft bed. The primary healing of the autografts was much weakened; there was suppression of the inflammatory processes that normally accompany healing and depression of epithelial mitotic activity. It appears that cortisone retards the rate of the processes which normally occur with healing, but does not alter them. The homografts in the cortisone-treated animals were found to provoke a relatively feeble and chronic reaction of uncertain progress, compared with the acute process seen in the controls. The inflammatory reaction was subdued and lymphocytic infiltration much less marked, but, again, the fundamental nature of these processes remains unaltered.

The authors suggest that these effects are partly due to the smaller blood supply and invasive activity which was noted in the autografts; other factors are the partial suppression of the immune response and the thwarting of inflammatory reactions by cortisone. On immunized animals, in the second experiments, homografts survived much less well under cortisone. Delay in the development of the immune state would, therefore, seem to be an important factor in the threefold or fourfold prolongation of the life of homografts by cortisone.

B. E. W. Mace.


Albino guinea-pigs in groups of five to fifteen were given 2 mg. wet weight B.C.G. vaccine intramuscularly and were tested for sensitivity 28 days later with tuberculin by a multiple-dose method. The animals were maintained on an ascorbic-acid-free basic diet, the vitamin being supplied by unlimited cabbage. The diameter of the tuberculin lesions after 24 hours was found to be proportional to the logarithm of the dose. By plotting the mean lesion diameter against the logarithm of the dose the position of the dose-response curve may be used to estimate the degree of sensitivity developed by the guinea-pigs.

A dose of 50 mg. propylthiouracil by mouth thrice weekly for 4 weeks had no effect on sensitivity by itself, but inhibited the desensitizing action of a single dose of cortisone (2 mg.) or of ACTH (1 international unit). A 28-day course of thyroxine sufficient to produce a mild thyrotoxicosis, caused a significant increase in sensitivity. If the thyroxine was given in an amount which did not cause any signs of thyrotoxicosis, it had no effect on the hypersensitivity, but it restored the desensitizing action of cortisone and ACTH in propylthiouracil-treated guinea-pigs. It was concluded that
thyroxine was necessary for the desensitizing action of cortisone and ACTH.

Norval Taylor.


The action of chorionic gonadotrophin on hyaluronidase was tested because there is amelioration of some of the collagen diseases during pregnancy. The spreading activity of hyaluronidase injected intradermally with Indian ink into mice was inhibited by chorionic gonadotrophin injections, but further investigation appeared to demonstrate that this action was not due to the gonadotrophin itself, but to contaminating adrenocortico- tropin.

First, the inhibition produced by chorionic gonadotrophin was qualitatively like that produced by adrenocorticotrophin and was similarly unaffected by gonadectomy or hypophysectomy, but was not produced after adrenalecomy. Secondly, the inhibitory activity of the gonadotrophin was unaffected by boiling, which destroys its gonadotropic activity but which does not destroy adrenocorticotrophic activity. Thirdly, the chorionic gonadotrophin when injected into hypophysectomized rats produced a fall in eosinophil cell count and in adrenal ascorbic acid content.

Adrenocorticotrophin has been detected in placenta, and this may be the source of that contaminating the chorionic gonadotrophin.

Peter C. Williams.


The action of cortisone on antibody formation in the rabbit was investigated by studying the recovery of the antibody titre after it had been depressed by injection of an adequate dose of antigen. Two groups of rabbits, eleven and twelve in number respectively, were sensitized to crystalline egg albumen and the theoretical total amount of antigen required for saturation of the antibodies was estimated from the antigen-antibody equivalence. After the injection the antibody titre and the leucocyte count were taken at 1 hour and then every 24 hours for 6 days. Subcutaneous injections of 10 to 25 mg. cortisone per kg. were given, starting 70 minutes after the shock dose and then 12-hourly for 6 days. In the controls the antibody titre fell to nearly zero for 24 hours with complete recovery in 6 days; it was associated with a neutropenia at 1 hour succeeded by a neutrophil leucocytosis at 24 hours with a lymphocytosis, the count returning to normal in 48 hours. The results differed in the cortisone-treated animals, the antibody titre being 17-2 per cent. of the initial level at 24 hours compared with 0-9 per cent. in the controls, and at 48 hours the titre was 36-3 per cent. as compared with 9 per cent. in the controls. Thereafter, the position was reversed, the titre rising from 39 per cent. at 72 hours to 110 per cent. at 120 hours in the controls, whereas in the cortisone-treated animals it rose from 43-5 per cent. to 56-4 per cent. There was a neutropenia in the cortisone-treated animals at 1 hour succeeded by an even greater neutrophil leucocytosis at 24 hours, while the lymphocyte count fell to 76 per cent. of the initial level and remained depressed during treatment.

Two phases of antibody response under cortisone were shown, the first phase lasting 48 hours during which the recovery of the antibody titre was greater than in the controls and was associated with a lymphocytopenia, followed by a second phase when the recovery was far less than in the controls. The initial rise corresponds with the fall in lymphocyte count, and the second phase may be explained by the demonstration by others that there is an inhibition of the antibody response when cortisone is given during the sensitization period, which suggests that the effect after 3 days is due to an inhibition of the reticulo-endothelial system.

**J. Pepys.**


Seven patients with advanced pulmonary tuberculosis were treated with ACTH or cortisone in an attempt to evaluate the participation of host mechanisms in tuberculous disease. In order that results should be placed entirely upon x-ray changes and other clinical factors which are difficult to assess, patients with active tuberculous laryngitis were included in the study. Each patient received 100 mg. hormone intramuscularly in four equally divided doses at 6-hourly intervals for an initial 10-day period: four patients received ACTH and three cortisone.

During the period of administration of hormones, rapid amelioration and subsequent disappearance of the constitutional manifestations of acute illness were witnessed. Patients became afebrile, but similar constitutional improvement was seen in two patients who were initially afebrile. In patients with laryngitis the symptoms abated at once, and subsequently the lesions were observed to become quiescent. Decrease in density of x-ray shadows was seen in five patients. Reversal of tuberculin skin sensitivity was observed in three out of the six patients tested.

On withdrawal of the hormone the signs and symptoms of acute illness rapidly returned and were as severe as or even worse than before. In the larynx, oedema and inflammation were complete on the first occasion should not be hormones. The return of tuberculo-protein skin sensitivity was delayed for several weeks after cessation of hormone administration. Within 3 weeks after the completion of hormone treatment significant increases, both in concentration of serum gamma globulin and in the titre of tuberculin haemagglutinating antibodies, were noted in three of the six patients.

Further administration of hormones demonstrated that the improved state was temporary and could not be indefinitely maintained. In two patients with laryngitis complete healing occurred after the administration of streptomycin: the bacilli in these two cases were subsequently found to be streptomycin-sensitive. The reaction of the group of patients as a whole to previous or subsequent streptomycin therapy does not emerge very clearly from the article, but the work was intended to evaluate the effect of the hormones given alone. It is pointed out that variations in the technique of hormone
ABSTRACTS


The authors state that toxaemia of pregnancy may perhaps in part be explained on the hypothesis that it is a manifestation of Selve's general adaptation syndrome, the stress being some unknown (possibly biochemical) factor related to pregnancy. Further, the somewhat conflicting evidence on the role of the adrenals in this condition might be held to justify a trial of cortisone. Fauvet noted that the adrenal glands were below normal size in fatal cases of eclampsia, and Fauvet and Munzer reported a low blood concentration of adrenocorticotrophic hormone in eclampsia. On the other hand Venning has brought forward evidence that the adrenals are hyperactive in normal later pregnancy, and Tobian has observed a high urinary level of mineral-controlling corticoids in pregnant women with oedema due to toxemia. There is, too, a clinical resemblance between toxæmia of pregnancy and intoxication with deoxycorticosterone (DCA), in both of which there may be oedema, hypertension, and albuminuria with a normal blood urea level. Also both conditions are improved by a low sodium intake and in both there may be exacerbations if sodium intake is excessive. If pregnancy toxæmia is, at least in part, due to excessive secretion of corticoids controlling mineral metabolism, it is possible that a relative deficiency of the gluco-corticoids may be a contributing factor.

It seemed unlikely to the authors that the administration of cortisone (in some respects a salt-retaininig hormone) would precipitate eclamptic convulsions by causing further water and salt retention, for diuresis and diminution of albuminuria has been noted by other workers from administration of ACTH and cortisone in acute nephritis and in nephritic patients with oedema.

The present paper describes the results obtained from the use of cortisone in eight cases of severe toxæmia. The preparation used was a microcrystalline suspension of cortisone acetate, 1 ml of which contained 25 mg. cortisone. It was given by intramuscular injection and the dose varied from 100 to 300 mg. cortisone acetate daily. Routine treatment with rest, sedatives, magnesium sulphate, etc., was given in addition. The authors claim that the need for sedatives was immediately reduced and that the period of gestation was prolonged by from 1 to 4 weeks, this enabling a viable infant to be born. They stress, however, that the "striking improvement" after cortisone was in the clinical condition of the patient. Headache was relieved, vision when affected was improved, restlessness was controlled, and both the patient and her friends were quite certain that she was much better. On the other hand the effect on blood pressure was disappointing. In two cases in which the oedema had been reduced its place was taken by ascites; in two others the oedema which had been diminished by cortisone later increased at the same time as the ascites became apparent. Altogether ascites developed in five cases. Seven of the patients were delivered of live babies, but two of these were premature and died. All but two of the patients survived.

[The abstractor has read all the eight case reports carefully and has failed to find convincing evidence that


In 1947 a female aged 64 who had had rheumatoid arthritis since 1935 was admitted to a sanatorium with active pulmonary tuberculosis. Tubercle bacilli were never found in the sputum, and she was discharged from the institution in 1948.

In 1950 she was readmitted: no change was noted in the radiological appearances and the results of further sputum examinations were negative. Because her joints were very painful, cortisone was given in the usual dosage. Her arthritis, and a secondary anaemia, improved considerably, but relapse occurred 3 weeks after treatment was stopped and a second course was started. After about 1,500 mg. had been given the patient had a haemoptysis. Radiological examination showed that there was now cavitation in the left apex, and for the first time the sputum contained tubercle bacilli. Streptomycin and D-p-amino salicylic acid were given, and 3 months later a radiograph showed that the cavity had almost completely healed.

In this case it appears that the administration of cortisone resulted in the reactivation of a previously well-healed tuberculous lesion. B. E. W. Mace.


The authors report their investigation of the effect of cortisone on pneumococcal bacteraemia. Into the ear vein of each of eight rabbits 1 ml of a broth culture of pneumococci was injected. The animals were paired, and one of each pair received cortisone while the other served as an untreated control. The treated animals were given cortisone in a dose of 15 to 20 mg. 20 hours and 1 hour before the injection of the culture, and 24 and 48 hours after the injection (if the animals were still alive). At varying intervals 1 ml of blood was withdrawn from the vein of the opposite ear and the number of organisms in the sample estimated by the pour-plaque technique.

In the control animals the number of organisms diminished rapidly; in the cortisone-treated group there was a slight initial fall, but thereafter a rapid increase, in the bacterial content of successive samples. The results of one experiment are given below.

<table>
<thead>
<tr>
<th>Time after Injection</th>
<th>Organisms per ml. (thousands)</th>
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<tr>
<td></td>
<td>Control</td>
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<tr>
<td>Immediately</td>
<td>5,600-0</td>
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<tr>
<td>10 minutes</td>
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<td>1 hr 20 min.</td>
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<tr>
<td>3 hrs</td>
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<tr>
<td>5 hrs</td>
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<tr>
<td>24 hrs</td>
<td>1-2</td>
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G. B. Forbes.

administration and the effect of their combination with other agents have yet to be evaluated. J. E. Houghton.


In 1947 a female aged 64 who had had rheumatoid arthritis since 1935 was admitted to a sanatorium with active pulmonary tuberculosis. Tubercle bacilli were never found in the sputum, and she was discharged from the institution in 1948.

In 1950 she was readmitted: no change was noted in the radiological appearances and the results of further sputum examinations were negative. Because her joints were very painful, cortisone was given in the usual dosage. Her arthritis, and a secondary anaemia, improved considerably, but relapse occurred 3 weeks after treatment was stopped and a second course was started. After about 1,500 mg. had been given the patient had a haemoptysis. Radiological examination showed that there was now cavitation in the left apex, and for the first time the sputum contained tubercle bacilli. Streptomycin and D-p-amino salicylic acid were given, and 3 months later a radiograph showed that the cavity had almost completely healed.

In this case it appears that the administration of cortisone resulted in the reactivation of a previously well-healed tuberculous lesion. B. E. W. Mace.
the administration of cortisone resulted in any benefit whatever. As to the authors' claim that it enabled pregnancy to be carried on for some weeks longer than would otherwise have been possible, the question arises whether this continuation was not sometimes, at least, at the expense of the well-being and even safety of the patient, and only to enable the cortisone trial to be extended. An example of this is in a case where there was retinal haemorrhage on admission, yet cortisone was continued for 8 days—that is, until the patient went into labour by spontaneous rupture of the membranes. She died 1 week later.] F. J. Browne.


The clinical features of a neuromuscular disorder which the authors call "menopausal muscular dystrophy" are described. They have studied twelve patients, of whom eleven were women, during the climacteric period or after. There was progressive weakness of muscles of the hip and shoulder girdles with little visible wasting, but a "soft" consistency of the affected muscles on palpation. There may be impairment of tendon reflexes associated with involved muscles: there has been no weakness of facial or bulbar muscles and no sign of involvement of the central nervous system. Creatinuria is surprisingly small. Biopsy examination of affected muscles shows a histological picture similar to that in $\alpha$-tocopherol-deficient animals, with degeneration of muscle fibres which are undergoing necrotic changes.

In some of these patients there was a good therapeutic response to wheat-germ oil orally, while five received cortisone with marked improvement in muscular power. When administration of cortisone was stopped the patients relapsed within a few days; these patients were accordingly given a maintenance dose of 100 to 150 mg. of cortisone every 2 days and apparently have remained well for a period of 6 months. J. W. Aldren Turner.


Forty-five patients with various neurological disorders have been treated with cortisone or with ACTH. In three cases of myotonia dystrophica, the myotonia was abolished during treatment with cortisone, but it returned when treatment was discontinued. No improvement was noted in the dystrophic process. In a case of myotonia congenita, the severe, generalized myotonia was abolished during treatment with ACTH; it returned, however, during treatment with DCA, and decreased again under treatment with cortisone. Three cases of myasthenia gravis received cortisone. In two instances the myasthenia became much worse during treatment. Symptoms returned to their previous level when the hormone was stopped, but there was no rebound improvement. These observations may be of importance from the viewpoint of mechanism of the disease. Three patients with dermatomyositis were improved by cortisone. The degree of improvement depends, however, upon the amount of fixed tissue damage. We now look upon these cases as medical emergencies.

A profound state of muscle dystrophy may occur during the course of acute disseminated lupus erythematosus. In one case this responded remarkably to cortisone. In another case the muscle weakness was unaffected by either ACTH or cortisone, although the constitutional symptoms, such as fever, were abolished. Three cases of amyotrophic lateral sclerosis and three cases of peripheral motor neuropathy were uninfluenced by cortisone. Two cases of Raynaud's disease were treated; in one patient with induration and ulcer formation on her fingers the skin changes cleared up, but the other patient who suffered from pure vasospasm was unaffected by the treatment. Two out of three patients with polyarteritis were improved by cortisone. Relapse occurred when the drug was discontinued.

No improvement was noted either in clinical symptoms of creatinuria in three cases of progressive muscular dystrophy of the childhood type. Seven out of eight cases of menopausal dystrophy have shown striking improvement with cortisone, but maintenance dosage is necessary.—[Authors' summary.]


In this paper are described studies of three diabetic patients who had developed a nephrotic syndrome, and of the effect of cortisone on glucose tolerance, oedema, and serum and urinary protein content. The cortisone was given intramuscularly, 100 mg. daily for 37 days. In two of the patients the insulin dose was adjusted to control the level of fasting blood sugar and the degree of glycosuria; in the third patient the dose of insulin was maintained at a constant level.

Apart from the expected decrease in glucose tolerance on starting cortisone therapy, the results were, in general, inconclusive. No consistent effect was observed on the level of serum proteins, cholesterol, or non-protein nitrogen, or on haemoglobin, and no change in blood pressure or in ophthalmoscopic appearances was observed. In all three cases there was an increase in the total daily urinary protein excretion. Ketonuria was only once observed, and then in slight degree.

Clinically, in only one of the three patients was there any improvement in the nephrotic state: this was only temporary and was followed by a fatal relapse. In this patient the insulin requirement was found to decrease from the third week of treatment onwards, and possible reasons for this unexpected effect are discussed.

B. E. W. Mace.

ERRATUM
