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", which appears for the second time in the present issue, 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 Mechanism and Prevention of the Rheumatic State.

The causal factors in rheumatic fever are an infective factor, probably Streptococcus pyogenes, acting on a genetically predisposed individual. The inherited factor determines an abnormal response to the infective agent. The abnormality consists in the production of a surfeit of antibody protein, excessive quantities of globulin both in the circulation and interstitially, and a resulting increase in blood volume. Evidence is reviewed bearing on the probability of these conclusions. The author recalls the commonly observed sequence of acute streptococcal sore throat, a lag period of about 2 weeks, then the first attack or a relapse of acute rheumatism; a rise in antistreptolysin O titre is also always observed. He refers to published genealogies suggesting that predisposition to acute rheumatism is transmitted by a recessive autosomal gene.

His own work, published in 1939, showed that at the beginning of rheumatic fever the apparent anaemia is a dilution phenomenon, essentially due to an absolute increase in the circulating plasma volume, and not to erythrocyte destruction. The serum was shown to have a high protein content, implying a great increase in total circulating protein. Rather more than twice the normal circulating globulin was present during active rheumatism, and the total circulating albumin tended to be somewhat below normal. The total circulating proteins remain at a high level during the height of rheumatic activity, and fall as the disease becomes quiescent. From this observation it seems improbable that the globulin mobilization is the antibody response to a specific rheumatic infection: for the rise begins before the onset of rheumatism, and does not increase during its course or persist in convalescence.

This leads the author to infer that the streptococcal infection merely fires off a chain of events, and has abated by the time that these events evoke the acute rheumatism. The new factor responsible for the rheumatic state is excess of antibody globulin, abnormal quantitatively and perhaps qualitatively because of the inherited predisposition. It is suggested that cortisone works through its function as an S hormone, affecting the conversion of protein into glycogen, that it has a bearing only on the inherited factor, and that the infective problem remains.

The following suggestions for the prevention of acute rheumatism are made. The children of rheumatic parents should be under the observation of public health officers. They should be housed in single bedrooms, employed in the fresh air and in small communities, nourished adequately, and educated to protect themselves from upper respiratory infection. Chemoprophylaxis should be applied at selected seasons. They should be advised never to marry a rheumatic subject, and to restrict their own families so as to be able to provide each child with a protected environment. Kenneth Stone.


The well-defined clinical and histopathological picture of acute rheumatic fever has led some clinicians, in Germany notably Graff and Aschoff, to suppose that it is an infectious condition due to some specific, as yet unidentified, organism. In Britain and the U.S.A., where the disease is much commoner, epidemiological, bacteriological, and serological studies have led to a different view and one which in German literature is propounded by Klinge and Rössle. These observers hold that acute rheumatic fever is a response, probably allergic, to a non-specific acute streptococcal infection. The following findings of the author support this view: the incidence of rheumatic fever ran closely parallel with that of scarlet fever. Each "epidemic" of rheumatic fever (in institutions) was preceded by an epidemic of sore throats. Serological examination with various anti-streptococcal antigens showed that the antibody titre rose even higher in patients with rheumatic fever than in patients with streptococcal infections not followed by rheumatic fever. It was proved that the prophylactic use of penicillin and sulphonamides for long periods in people prone to rheumatic fever reduced considerably the incidence of relapses.

It is not known why some people develop acute rheumatism, scarlet fever, erysipelas, or nephritis in response to a streptococcal infection; presumably the
difference lies in the constitution of the individual, and this may account for the observation that scarlet fever generally attacks large, healthy, robust children, whereas those with rheumatic fever tend to be below average size and of poor physique. Marianna Clark.


A study was made of 140 rheumatic children, aged 6 to 16 years at the St. Francis Sanatorium, Long Island. Different observers assessed the degree of rheumatic activity and severity of the cardiac lesions, and the electrocardiographic findings. The duration of electrical systole, corrected for rate (QTC), was determined according to Bazett’s formula several times for each child: 0.405 sec. was taken as normal; 0.44 sec. would be considered a moderate prolongation.

The larger group of 123 children was observed throughout a single admission period averaging 12 months for each child. In 33 the QTc was initially normal or only moderately prolonged; it became shorter during the stay in hospital: only a fifth of these had progressive heart disease. In 39 the QTc remained unchanged, and in a third of these, in whom the QTc was also prolonged, there were progressive heart lesions. In 51 the QTc became longer while in hospital: three-quarters of these had progressive heart disease. Where the QTc was initially prolonged as well as increasing, nineteen out of twenty had severe and progressive lesions: four of these died. The smaller group of seventeen children was observed over intermittent admission periods for an average total time of 43 years per child. Where the QTc was little if at all prolonged and tended to become shorter, cardiac lesions were unimportant; but where QTc was initially considerably prolonged and tended to become still longer, lesions were or became severe.

The authors conclude that serial observations on the corrected systole time have a prognostic value. The prognosis is bad where systole remains prolonged over a long period of time, especially if it becomes progressively longer.

J. A. Cosh.


The authors determined the Q-Tc (Q-T interval corrected for cardiac rate) by Bazett’s formula in 27 children with acute rheumatism, all but two having evidence of carditis, and in 25 controls. They consider 0.422 to be a satisfactory figure for the upper limit of normal, as in 23 of the 25 controls the value of Q-Tc was below this. Of the 25 patients with active carditis, in 21 the Q-Tc was greater than 0.422 on at least one occasion. A persistently increased Q-Tc is considered by the authors to indicate a continually active carditis and to be of corresponding prognostic value [although the supporting evidence given is not convincing].

J. A. Cosh.


The serum antihyaluronidase level was determined in 705 children by the mucin-clot prevention method of Quinn. There were considerable variations in healthy children, but on average the titre increased with age. The estimation was carried out on eleven children with active rheumatic fever and in ten of these high titres were found, but in only three cases was the titre above the highest found in healthy children. The author concludes that the test may give useful confirmatory evidence in the diagnosis of rheumatic fever, but that it is certainly not diagnostic of the condition. It seems that the titre fell when the activity subsided, or when chemoprophylaxis was given. R. S. Illingworth.


The association of rheumatic fever and glomerulonephritis has been investigated in 117 patients suffering from glomerulonephritis and in 188 post-mortem records of cases of rheumatic carditis. In the former series there was a total incidence of 6 per cent. of poly-arthritis or rheumatic heart disease, and in 2-5 per cent. active rheumatism and nephritis co-existed. From records of the cases of rheumatic carditis it was found that five of the subjects had had acute glomerulonephritis at death, four chronic nephritis, and seven a proliferation of glomerular epithelium, but not sufficient to warrant the diagnosis of glomerulonephritis. Henry Cohen.


Efficient salicylate therapy of rheumatic fever depends on correct selection of cases and an adequate level of the substance in the blood. The minimum level is 35 mg per 100 ml. blood and must be reached quickly and maintained for some time. The rapid increase necessary can only be obtained by intravenous therapy.

The attainment of an effective blood level depends essentially on the degree of intolerance. Symptoms of indigestion prevent peroral exhibition of single doses as large as 2 g. or daily doses over 8 g., while such therapy for more than 3 days is generally impossible. Salicylate may be given successfully per rectum as an isotonic solution or in gruel in order to diminish the local irritation. By the rectal route single doses of up to 8 g. in isotonic solution or 5 g. in gruel, and daily doses of up to 16 g. (divided into two or three parts), can be given. By this means maintenance of an effective blood level is possible. By intravenous therapy only 2 g. in 10 per cent. solution can be given as a single dose. Repeated injection of 1 g. sodium salicylate, however, produces an effective blood level. The ethanolamine salt of salicylic acid gives a more persistent blood level with correspondingly fewer injections. The diminution of gastric upset when sodium bicarbonate is given is of no value, for the blood level remains low due to increased excretion.

Ideal blood levels may be obtained by an initial intravenous dose followed by maintenance by the rectal route. On subsidence of the acute stage, peroral therapy may be instituted. Observation of the serum salicylate level is essential in salicylate medication because the drug as a rule should be administered until the limits of tolerance are reached.

Norval Taylor.


Chronic Articular Rheumatism (Rheumatoid Arthritis)


Of thirty patients with rheumatoid arthritis treated with "salazopyrin" (salicylazosulfapyridine), one had to stop treatment because of the sudden onset of anaemia and another refused to continue after 2 days because of "nervousness"; fourteen gained no benefit, but in fourteen there was marked improvement. The ages of the last group (in five of whom the presence of ankylosing spondylitis was recorded) varied from 24 to 64 years, and the duration of illness from 1 to 15 years; daily doses of 1-5 to 4 g. salazopyrin were given for periods of 2 months to 1 year, all but one of the group being still in receipt of a daily maintenance dose. Improvement, shown by diminution in joint swelling, stiffness, and pain, always began during the first 7 to 14 days of treatment. All these patients became worse when treatment had twice to be interrupted because of a shortage of salazopyrin. Toxic effects included restlessness and sleeplessness, mild nausea, and, in one case, a skin rash; the authors state that in only one case (that referred to above) was there a toxic effect on haematopoiesis [although in one of the group improved by treatment a reduction in erythrocyte count and haemoglobin concentration is shown]. No significant effect was observed upon the erythrocyte sedimentation rate.

When salazopyrin was added in a concentration of 0-5 per cent. to the food of rats injected with the L-4 strain of pleuroneumonia-like organism (which produces a polyarticular arthritis) the incidence of arthritis was very slightly lower, and the survival rate higher, than in the control animals; when the concentration was raised to 1 per cent. and 3 per cent. the incidence of arthritis was higher than in the controls. Other rats and mice given 1 per cent. salazopyrin for periods up to 121 days showed no consistent variation in body weight or leucocyte count compared with untreated controls.

[The discrepancy between these results and those of Sinclair and Duthie (Ann. rheum. Dis., 1949, 8, 226) is attributed to the smaller and more prolonged dosage used in the present study; since improvement was always apparent within 2 weeks this explanation seems inadequate. In the absence of controls or of any quantitative measure of improvement the significance of these clinical results is debatable.] H. McC. Giles.


Calciferol was used in the treatment of eight cases of tuberculous peritonitis and the results were encouraging. It was found that the response to treatment was as good with small doses (3,000 units daily) as with massive doses (150,000 to 180,000 units daily). Improvement was seen in the patient's general condition, in a fall in erythrocyte sedimentation rate, and in return of body temperature to normal. The blood calcium level rose in all cases irrespective of the dosage; changes in phosphorus and non-protein nitrogen levels were less consistent; in some cases there was a fall in phosphorus level despite hypercalcaemia. The results obtained in two cases of chronic rheumatoid arthritis of doubtful tuberculous aetiology were also favourable. Daily calciferol was combined with injections of streptomycin.

J. T. Leyberg.


A patient developed polyneuritis after receiving 100 mg. "myochrysine" each week for 9 weeks. The symptoms consisted of tingling in the extremities with muscular weakness and incoordination. The cerebrospinal fluid was normal. The condition became worse for about a month after administration of myochrysine ceased and thereafter gradually improved with complete recovery by 4 months later.

V. J. Woolley.


Anaemia, either hypochromic or normochromic in type, is found in association with all forms of infection. It is common in rheumatoid arthritis. Sinclair and Duthie in 1949 described the response of 23 cases to intravenous iron; they have now treated a further 28 cases, making 51 in all. These patients all proved resistant to oral iron. A satisfactory rise in haemoglobin value was found in 38 cases but thirteen remained refractory and only the remaining 13 showed any benefit from oral iron. In a further thirteen cases the haemoglobin level was maintained for as long as 23 months without further treatment and three cases which responded initially required a further dose. Ascorbic acid given intravenously was without effect on the refractory cases. The authors consider that iron absorption, as measured by the effect of oral iron on the plasma iron level, was normal even in refractory cases. They conclude that the anaemia is due to an increased need of the tissues for iron, a need which cannot be met by absorption of iron given by mouth. It is clear that experimental observations with radioactive iron might throw interesting light on the mechanism of this type of anaemia. The cases which responded to oral iron showed a rapid fall in the erythrocyte sedimentation rate. It is suggested that the anaemia alone cannot account for the high rate and that there must be some associated change in serum protein levels. Apart from interesting theoretical considerations raised by this paper, it is encouraging to know that in some cases of
rheumatoid arthritis the anaemia can be relieved, a finding which is not corroborated by the work of Wintrobe and his colleagues (J. clin. Invest., 1950, 29. 1505).


Biopsy of striated muscles revealed an arteritis in five out of 57 cases of rheumatoid arthritis. The lesion was not directly connected with the affected joints, as the portions of muscle sectioned were taken at areas remote from them. A specific lesion is thought to have been found in view of the constancy of its anatomical location and because similar lesions were not encountered in other conditions. The vessels involved were large arterioles or small arteries. The histological features were not distinctive, and consisted of a granulomatous inflammation which might be localized in the adventitial or extend through all three arterial coats. Neither endothelial destruction nor collagenous necrosis was seen and thrombosis did not occur. In discussing the lesion a useful comparative table is given showing the main differences in several types of arteritis.

It is unlikely that this lesion will be of diagnostic value in view of its infrequency and the fact that only a few of a large number of serial sections showed the histological changes. This probably accounts for the negative findings of earlier workers.

G. J. Cunningham.


The possibility of a connexion between plasma cells, antibody formation, and hyperglobulinaemia was studied in the Department of Medicine, Cambridge University. In ten consecutive cases of rheumatoid arthritis of variable duration and severity, bone marrow was examined, plasma protein levels were estimated by a micro-Kjeldahl technique, and erythrocyte sedimentation rate was measured. The plasma-cell elements of the marrow were classified as plasmablasts, proplasmacytes, plasmacytes, plasma cells showing early homogeneous degeneration, and degenerative plasma cells. The proportion of all plasma cells in the preparations was 1.8 to 6.3 per 100 marrow cells. A finding of more than 2 per cent. is certainly abnormal, but even figures higher than 3 per cent., the presence of nuclear and cytoplasmic abnormalities in plasma cells, and the finding of multinucleated cells are not absolutely diagnostic of multiple myelomatosis without supporting evidence. A definite increase in the plasma globulin level was noted in every case. It is suggested that the hyperglobulinaemia of rheumatoid arthritis is an antibody response, accompanied by plasmacytosis, to an unknown antigen.

[These findings agree substantially with those of Leitner, Britton, and Neumark (Bone Marrow Biopsy, 1949). It is probable that plasma cells are concerned with the production of globulins.] E. Neumark.


Felty’s syndrome is defined as a triad of rheumatoid arthritis, splenomegaly, and neutropenia. This association of signs had been noted by many workers long before Felty (1924) recognized it as a clinical entity and gave a description of five cases in middle-aged men and women. The paper deals with four cases, one male and three female. Splenectomy was performed in all of them with good results. The most striking feature was the improvement in general health, which was found to be maintained a year later. Eye complications such as corneal ulcer and hypopyon tended to clear up, ulcers in the mouth and on the legs healed well. The leucocyte count was restored to normal, which is held responsible for most of the improvement. The arthritis also improved. Some of the features of the syndrome are ascribed to hypersplenism, whose modus operandi is discussed. The authors urge the use of splenectomy in Felty’s syndrome, unless there are definite contra indications.

D. Freiskel.


The radiological appearances of the manubrio-ster nal joint in a series of 61 cases of ankylosing spondylitis are described, comparison being made with a similar group of healthy persons and a smaller group of patients with polyarticular rheumatoid arthritis. Narrowing and eventual fusion of the joint were found in a high proportion of the patients with spondylitis, all those over 35 years of age showing this feature. The changes in the manubrio-ster nal joint are regarded as similar to those found in the sacro-iliac joint.

The superficial location of the manubrio-ster nal joint made it possible to undertake biopsy examination in 16 cases, including one in which the joint was fused. The cartilage was found to be replaced by fibrous tissue which involved the adjacent bone ends, but which did not show any inflammatory reaction.

H. A. Sisson.

(Osteo-Arthritis)

Denervation as Treatment for Arthritis Deformans Coxae. [In English.] HIERTONN, T. (1950). Acta orthopæd. scand., 26, 64. 5 figs, 39 refs.

All the recent literature on the anatomy of the nerve supply to the hip-joint is surveyed.

Obturator neuromyotony or resection alone is insufficient to bring about adequate relief of pain in arthritis, be it “primary” or secondary to such conditions as subluxation, slipped femoral epiphysis, or unhealed arthrodesis. There are cases, however, where the more radical operations of arthrodesis and arthroplasty with total capsulectomy are not indicated, especially in patients too old or frail to withstand major operations or those with a good range of movement.

The author treated 54 patients by denervation at the Karolinska Institute, Stockholm, one patient undergoing bilateral denervation. All patients underwent obturator neuromyotony, combined with section of the nerve to the quadratus femoris and gemellus inferior. This latter nerve supplies part of the posterior aspect of the joint. At 43 operations the obturator nerve was carefully dissected out by an anterior intrapelvic, extraperionidal approach, combined with posterior operation through a transverse incision across the buttock, through the glutus maximus and with medial retraction of the
sciatic nerve. These patients fared somewhat better than those who had undergone simple division of the two nerves without careful search for all branches given off high up. All the same, only in 50 per cent. of cases was improvement noted and in no case was complete sensory denervation of the joint achieved.

Elliott E. Philipp.


A series of 24 cases of arthroplasty of the hip carried out by the Smith-Petersen technique at the Sophies Minde Clinic for Cripples, Oslo, is reviewed. The average age of the patients was 42-25 years, the youngest being 17 and the oldest 63. Six patients with bilateral arthritis, who had undergone operation only on one hip, showed marked clinical deterioration in the side which had not been operated upon. Results were excellent in four cases, satisfactory in 31, and unsatisfactory in six. In one case, the condition was worse. The presence of a few degrees of hyperextension at the hip is more important for walking than is a marked degree of flexion. The best indication for the operation is unilateral arthritis in a patient with a sedentary occupation and severe symptoms. Gables show the degrees of movement obtained and the functional results.

Elliott E. Philipp.

(Spondylitis)


In a series of 100 patients with Marie-Strümpell arthritis valuable results were obtained with radiotherapy. This treatment is used at any stage in the disease and an increase in mobility can be expected in a fair percentage of the mild and moderately advanced cases. In the mild and moderate cases they discovered fifteen out of 47 patients in whom the x-ray appearances improved under this treatment. John Charnley.


A Chinese business man aged 26 who suffered from a seriously deformed spine and hip joints for a number of years, was diagnosed to have ankylosing spondylitis. He suffered concurrently from repeated attacks of iritis. The articular as well as ocular findings are recorded in detail. The possibility of iritis as a pointing sign in this type of joint disease is suggested. (Authors' summary.)

(Miscellaneous)


The authors have confirmed the work of previous investigators on the lupus erythematous (L.E.) phenomenon (presence of L.E. cells with the formation of clumps and rosettes in the blood). The phenomenon is not an artefact and is unrelated to the addition of anticoagulant.

Serum from patients with chronic discoid or disseminated discoid L.E. does not produce the phenomenon, nor does serum from other diseases in the so-called collagen group or from samples of blood with a high-titre syphilitic reaction. The L.E. phenomenon is a constant observation in acute lupus erythematosus in the active stage; it may be useful in diagnosis of fever of unknown origin. Previously undescribed inclusion bodies of oval shape are presented and are thought to be stages in the development of the L.E. body; two tests are described whereby L.E. cells can be induced to develop in normal leucocytes.

Sternal marrow in cases of subacute lupus erythematosus disseminatus usually gives negative results, but in some cases the blood serum may give definite positive results.

G. A. Hodgson.


The ground substance of collagen is closely related to heparin. In collagenous diseases it is presumed that there is circulating in the blood a substance antagonistic to this ground substance and therefore to heparin. Investigation of ten patients with acute lupus erythematosus showed that the blood contained a factor which inhibited the action of heparin to the same degree as that found in rheumatic fever. The bearing of this upon cortisone therapy is discussed.

John T. Ingram.


The author has studied the effect of tonsillectomy in cases of polyarthritis. Of 860 patients (283 males and 577 females), 432 (149 males and 283 females) underwent tonsillectomy. A careful history was taken of ear and throat conditions, especially of throat infections; a positive history and, in some cases, a raised erythrocyte sedimentation rate influenced the decision to operate. In 164 cases the tonsils were examined histologically and on the basis of the pathological findings the cases were divided into two groups: (1) 110 cases with definite signs of inflammation of the tonsils; (2) 54 cases with signs of hyperplasia only, and little or no inflammatory change.

On studying the incidence of these findings as regards positive and negative pharyngeal histories the authors concluded that even with a positive tonsillar history it was not possible to form any definite opinion what the pathological findings would be. No statistically significant difference in the mean erythrocyte sedimentation rate was found between the tonsillectomy group and the control series, even when the cases were classified as regards positive and negative pharyngeal history and positive and negative tonsillar findings.

The author points out that American investigators have recently advanced the view that chronic polyarthritis is probably associated more with metabolic disturbances rather than with infectious conditions. No significant difference was noted in the tonsillectomy series as regards the joints involved on the patient's admission to and discharge from hospital.

E. D. Dalziel Dickson.

Serum gamma globulin and antistreptolysin titre were estimated in 78 patients with rheumatic conditions, and in 35 normal controls. The mean level of gamma globulin in normal subjects was 0.882 G. A gamma globulin value of over 1.0 G was found in most patients with rheumatoid arthritis and rheumatic fever. The antistreptolysin titre was invariably raised in rheumatic fever, but only about a quarter of the patients with rheumatoid arthritis showed a similar rise.

The authors conclude that there is no correlation between these two values, and that the gamma globulin estimation is only of limited value: its estimation is a complex procedure.

B. E. Mace.


Sciatica


In this paper, an attempt is made to correlate physical signs seen in patients with sciatica with the findings at operation and the subsequent progress. The close correlation between limitation of straight-leg-raising (S.L.R.) and limitation of forward flexion of the trunk on standing is demonstrated, and patients seen are classified in three ways: (1) Those in whom there is marked limitation of S.L.R. and of forward flexion; in this group disk prolapse is nearly always found at operation and subsequent progress is good. (2) Those with little or no limitation of S.L.R. and forward flexion; these commonly do not show a disk prolapse or obtain relief from laminectomy. In these patients the sciatica is assumed to be due to stretching of an abnormally sensitive nerve root. (3) Those with marked discrepancy between limitation of forward flexion and S.L.R. These rarely show a disk prolapse and do badly after operation; it is suggested that some of these patients are psychoneurotics.

The reversal of the normal lumbar lordosis is ascribed to the wedging effect of the posteriorly projecting disk rather than a reflex mechanism to relieve tension upon the sciatic nerve. Scoliosis, which is seen in many of these patients, is often transitory and seems by itself to be of little significance.

A method of establishing an axis of flexion for the lumbar spine as a whole is described, and from radiographic measurements of movements in the cadaver it is stated that this axis lies in the posterior quarter of the intervertebral disk. Flexion and extension of the spine thus cause little change in the position of the dura and nerve roots, and the tension placed on the sciatic nerve either in straight-leg-raising or in forward spinal flexion is due to flexion at the hip joint. This stretching is maximal in the arc 40 to 60°. *Peter Ring.*

Non-Articular Rheumatism


In 1945 the author described several cases of scapulo-humeral periarthritis, the condition being associated with prolonged fever, loss of weight, and a high erythrocyte sedimentation rate. He has now analysed all cases of this condition admitted to one of the medical units of the Bispebjerg Hospital, Copenhagen, between 1945 and 1950 (a total of 82 cases), in order to establish the incidence of generalized symptoms and signs.

In sixteen cases there was low fever, a temperature of about 38° C. (100-4°F.) lasting for at least several weeks and in some cases for 6 months and even longer. The erythrocyte sedimentation rate was raised in 32 cases, in 24 of them above 50 mm. in one hour. In no less than sixteen cases the condition complicated thyrotoxicosis. Fleeting pains in various parts of the body often preceded the local condition, and soft-tissue involvement in the hands, including contractures, is also described.

W. G. Harding.

Tendovaginitis Stenosans (Maladie de Quervain). Muller, H. (1950). *Arch. chir. neer.*, 2, 188. 4 figs, 11 refs.

The author surveys the literature and reports eight cases of typical Quervain’s disease and one case of stenosing tendovaginitis involving the second and third compartments of the carpal ligament. The author supports the view that the primary changes are in the dorsal carpal ligament, and he stresses that a portion of the tendon sheath should be removed. *J. Agerholm.*


General Pathology


The degenerative changes associated with the ageing process in the spinal column were studied in forty unselected cadavers, 35 male and five female. The spinal columns were inspected after division by a mid-sagittal
ABSTRACTS


The author describes the results of an investigation into the effects of various diseases on the level of non-specific inhibitor of hyaluronidase in serum as estimated, by the viscosimetric method of Glais and Glick (J. invest. Derm., 1948, 11, 259). The blood level of hyaluronidase inhibitor was measured in 27 cases of polyomylitits and the results compared with those in thirty normal subjects. A significant elevation above the normal was found, and follow-up studies on nine patients showed that the magnitude of the inhibitor value was proportional to the severity of the disease. Similar results were obtained on three monkeys and 128 mice which had been experimentally infected. In order to test the specificity of this phenomenon measurements were made on 127 patients exhibiting a wide variety of bacterial and virus diseases and the values compared with those obtained from 211 normal sera. It was concluded that the elevation of inhibitor values in blood serum in infectious diseases was non-specific, but that an essential requirement for elevation was acute systemic involvement. The effect of vaccinia vaccination on the serum inhibitor level of 35 college students was also studied; in sixteen individuals with immune reactions negligible changes in the inhibitor level were observed, but in the other nineteen subjects the magnitude of the elevation paralleled the intensity of the reaction.

The author found a significant elevation of serum inhibitor level in twenty cases of acute rheumatic fever and again in ten cases of acute streptococcal pharyngitis. Subnormal inhibitor values were observed in ten cases of convalescent rheumatic fever and in fifty cases of inactive rheumatic fever; it is suggested that the lowered inhibitor level might be a factor in enhancing the susceptibility of these patients to rheumatic disease. In five children suffering from hypoglycaemia and treated with 9 mg. adrenocorticotrophin (ACTH) every 6 hours over a 4-day period, it was found that a significant rise in the serum inhibitor level was produced by the ACTH treatment and that it reverted to slightly below the pre-injection level 7 days after the termination of hormone therapy. The abnormally high serum inhibitor levels found in cases of rheumatic fever were reduced to normal during ACTH treatment, but rose again when therapy was discontinued. Significant elevations of serum inhibitor level were observed in animals subjected to stress, and it was found in rats that adrenectomy abolished the rise in the serum inhibitor level normally caused by chilling. It was concluded that the adrenal cortex may play an essential role in controlling the fluctuation of serum hyaluronidase inhibitor level.

An investigation of the occurrence of hyaluronidase in human malignant tissue was undertaken, and clean, non-necrotic specimens of tissue obtained under sterile conditions from four benign and six malignant tumours were extracted under aseptic conditions. Specimens from 25 malignant tumours and 25 specimens of normal tissue which were directly contaminated by bacteria were also extracted, and it was found that neither benign nor malignant tumours possessed any hyaluronidase activity other than that contributed by microorganisms containing the enzyme. Significantly high serum concentrations of hyaluronidase inhibitor were found in 32 cases of malignant tumour which had undergone metastases, as compared with 75 normal subjects and 25 cases of benign and thirty of malignant but non-metastatic tumour. It was concluded that elevation of the serum inhibitor level occurs in cancer only when the disease has progressed to the stage of a systemic reaction.

M. J. H. Smith.


A simple method is described for the extraction of cortisone-like material from urine. The material is injected into adrenalectomized mice and its effects on the number of circulating eosinophil cells is measured. Preliminary results showed that cortisone-like activity was absent from the urine of patients with Addison's disease and hypopituitarism but increased during ACTH administration, in late pregnancy, and in a patient with an adrenal cortical carcinoma.

A. C. Crooke.
ANNALS OF THE RHEUMATIC DISEASES


Male and female albino rats of the Fairfield strain, weighing 125 to 250 g., were used. The animals received 0.2 mg. adrenaline per kg. subcutaneously and were then restrained in a tail cage for 4 hours. Eosinophil counts were made by a modification of the Randolph technique (J. Allergy, 1944, 15, 89) on tail blood at 10 minutes, 2 hours, and 4 hours after the injection. A total of 0.57 c.mm. blood was counted in aequous 50 per cent. propylene glycol with 0.1 per cent. eosin.

Single-stage adrenalectomy was performed under ether, the time required to complete the operation being measured from the time the animal was first picked up to the clamping of the second adrenal pedicle.

It was found that an eosinopenia followed stress even though adrenalectomy was complete within 10 minutes, and that the continued normal 4-hour fall in circulating eosinophils took place in the absence of continued secretion of the adrenal cortex. Norval Taylor.


By means of parallel biological assays the amounts of adrenaline and noradrenaline in the adrenal glands of the rabbit and in adrenal venous blood before and during splanchnic stimulation were estimated. Adrenal glands were taken after death, the capsule removed, and the gland ground with sand and 10 ml. 0.1N hydrochloric acid per g. The extract was filtered and assayed. Adrenal blood was collected in eviscerated rabbits anaesthetized with urethane from a cannula in the vena cava between ligatures which closed all veins other than the left adrenal vein. The blood was rapidly cooled and centrifuged and the plasma assayed.

The tests employed were on: (1) fresh rabbit ileum, which was twice as sensitive to adrenaline as to noradrenaline (A/N ratio 0.5); (2) rabbit ileum stored 4 days at 4°C. (A/N ratio 3.0); (3) blood pressure of rabbit anaesthetized with urethane, treated with cocaine 8 mg. per kg., and with the vagi cut (A/N ratio 0.5); (4) isolated rectum of week-old chick (A/N ratio 0.05); (5) isolated uterus of rat in dioestrous (A/N ratio 0.02).

The sympathetic obtained was principally adrenaline. This was the case with sympathin extracted from the gland and also with that from the adrenal venous blood. In ten rabbits when the left gland was stimulated before it was removed the mean concentration of adrenaline was 568 mg. per g. compared with 418 mg. per g. in the right (range 400 to 890 mg. and 225 to 756 mg. respectively). In nine rabbits where neither gland was stimulated the means were: left 472, right 498 mg. per g. Noradrenaline was detected only twice, each time in unstimulated glands and amounting to about 10 per cent. of the total sympathin. In twelve rabbits the mean adrenaline concentration in plasma from the adrenal vein was 0.084 mg. per ml. Noradrenaline was detected in plasma from three of the rabbits in concentrations of 0.02, 0.01, and 0.03 mg. per ml. During splanchnic stimulation the amount of adrenaline rose and noradrenaline was detected more often. The amount of noradrenaline was greatest in the samples collected between the 9th and 12th minutes of stimulation, when the percentage of adrenaline fell to 68. Adrenaline only was detected after the 18th minute of stimulation. R. P. Stephenson.


Twenty rats were given a 2 per cent. sodium chloride solution instead of drinking water, and all developed hypertension and cardiac hypertrophy at the end of 6 weeks. The animals were further subdivided into two groups of twelve and eight, the first being subjected to bilateral adrenalectomy, and the second to an equivalent operation in which the adrenals were manipulated but not removed. After the operation, the rats continued on sodium chloride and, at the end of 4 weeks, it was noted that the blood pressure both in sham-adrenalectomized controls and in adrenalectomized animals remained at a comparable high level. It is concluded that salt hypertension, once established, persists in spite of total adrenalectomy. Furthermore, in the adrenalectomized rats cardiac hypertrophy disappeared despite the persistence of hypertension. In other experiments it was shown that salt hypertension is a reversible process and can be made to disappear by replacing sodium chloride with tap water. In a group of seven salt-induced hypertensive rats, bilateral nephrectomy was performed. The hypertension persisted as long (about 3 days) as the animals survived.

It appears that salt-hypertension in rats is not mediated through the adrenal gland or kidney. A. I. Suchett-Kaye.


The sources of error inherent in the chamber eosinophil count are described: 99 per cent. of observations in 183 successive clinical determinations were found to lie within the expected limits as calculated from the formula. The theoretical limits of chance variation in differential eosinophil counts in marrow smears were calculated with the chi-square formula, but the observed errors exceeded this estimate, a finding attributed to clumping of eosinophils. Peripheral eosinopenia induced by adrenocorticotropic (ACTH) was not accompanied by any significant change in marrow eosinophils.

The physiological variations in eosinophil counts are reviewed. Serial counts show a significant diurnal variation with considerable minute-to-minute fluctuations superimposed upon it; 38 per cent. of normal subjects had a maximum morning fall of eosinophils of at least 50 per cent. A single eosinopenic response to ACTH or adrenaline is not an unequivocal test for the integrity of the hypothalamus-pituitary-adrenal chain, and repeated and controlled observations are necessary. Ephedrine was as effective an eosinopenic agent as adrenaline.

P. C. Reynolds.


Severe disturbance of liver function is rarely found in patients suffering from rheumatism, and milder changes are not uncommon. The author describes 76 cases of...
rheumatoid arthritis which were investigated from this point of view. In fifteen cases, in seven of which there was no heart lesion, the liver showed marked enlargement, but in all it returned to normal on recovery. In 66 cases there was disturbance of water metabolism, the 24-hourly output being only 65 to 75 per cent of the intake, and recovery was followed by diuresis. In 59 cases McClure's blister test was positive. The surface tension of the urine was lowered in 66 cases, due in all probability to the presence of bile acids. Ehrlich's aldehyde reaction for urobilinogen was positive in 54 cases, and the Takara-Ara reaction in thirteen. These returned to normal after recovery.

L. Firman-Edwards.


Prolonged exercise of guinea-pigs did not produce any conspicuous morphological changes in the Achilles tendon, though a chemical analysis showed an increase of mucopolysaccharides.

J. Agerholm.


Previous observations had shown that the medullary cavity is in some places in direct contact with the basal part of the articular cartilage without any intervening bone lamella. When rice starch was injected into the medullary cavity of the epiphyses of newly-killed rabbits, starch grains were found in the basal and central parts of the cartilage. If the joints were subjected to repeated compression after the injection, most of the grains were found in the upper and medial portion of the articular cartilage, and some were found in the synovial fluid. The findings were similar when the starch was injected intravenously in live rabbits. Similar contacts were found in man as well.

Special radiological investigations proved that the thickness of the articular cartilage rapidly increases when the joints are subjected to repeated compression and that it decreases when this stress ceases. Normal and pathological knee-joints were examined in this way.

J. Agerholm.


Estimations of the hyaluronic acid content, the viscosity, and the protein content of synovial fluids were carried out in man and animals. The high viscosity of the synovial fluid is due to its content of hyaluronic acid and is approximately in inverse proportion to the volume of fluid. In pathological joints the protein content was found to be low in degenerative conditions, moderately increased in traumatic ones, and greatly increased in rheumatic and infective arthritis, while the hyaluronic acid content was found to be low in the traumatic effusion and relatively high both in degenerative and in infective rheumatic arthritis.

J. Agerholm.


The protein content of normal synovial fluid is 1 to 2 g. per 100 ml. In 45 pathological cases it was found to be about 6 g. per 100 ml in infective and about 4 g. per 100 ml in non-infective exudates. Qualitative analysis by electrophoresis showed that in acute exudates the relative concentrations of the different protein components corresponded to those of plasma, but in chronic exudates that of fibrinogen was reduced and eventually disappeared and that of gamma globulin was increased.

J. Agerholm.

ACTH, Cortisone, and Other Steroids


The anti-rheumatic properties of cortisone and pituitary adrenocorticotrophic hormone (ACTH) have been confirmed by several groups of investigators.

During the time of their administration, these hormones have exerted a decidedly suppressive effect on the clinical and biochemical manifestations of rheumatoid arthritis. When the use of the hormones is discontinued symptoms recur rather promptly in most cases, but in several of our cases pronounced improvement has persisted for several (7 to 14) months. The optimal dosage and methods of administration of these hormones for the investigative management of a chronic disease such as rheumatoid arthritis remain to be determined. Several schemes are under investigation. Rather prolonged relief with minimal side effects has been provided in some cases by the continued use of small maintenance doses after the earlier use of larger suppressive doses.

Cortisone or pituitary adrenocorticotrophic hormone generally abolishes quickly the manifestations of acute rheumatic fever. There is reason to believe that the lesions of acute rheumatic carditis also are suppressed, in consequence of which the prevention of certain chronic cardiac lesions may be anticipated with some confidence, especially if adequate hormonal usage during the acute rheumatic state is followed by prolonged chemophobia-laxis (for example, with penicillin given orally). The articular complications of disseminated lupus erythematosus and psoriasis are responsive to these hormones. Limited results were obtained in 2 cases of tuberculous arthritis.

These hormones are powerful agents which may affect many functions and tissues of the body besides those of joints and muscles. Their prolonged use, at least in certain doses, may produce certain undesirable effects. These side effects have, to date, been transient and reversible. Certain measures have been developed to minimize or control some of them, but these effects still constitute an important problem for further investigation. If control of the side effects is not adequate in any given case, smaller doses of the hormones should be used and patient and physician alike should be content with a reduced amount of symptomatic relief.

With the exception of 17-hydroxy cortisol (compound F of Kendall), none of the currently available...
The author puts forward his reasons for believing that cortisone may be a more effective therapeutic agent than ACTH in gout, and suggests that it may prove in the future to be an important means of preventing this condition from progressing to the tophaceous stage. He points out that although the method by which colchicine effects relief in acute gout is unknown, there is good reason to assume that when given with cortisone or ACTH it exercises a synergistic action and produces remissions after the withdrawal of these substances.

W. S. C. Copeman.


Two male patients suffering from spondylarthropathies and renal diabetes were placed on a standard diet and given Armour ACTH 60-100 mg. daily for a fortnight. The period of investigation was preceded and followed by control periods of one week each. The dose of ACTH was divided into three parts and administered half-an-hour, 5 hrs, and 9 1/2 hrs after breakfast. The patients were confined to bed except for one hour daily.

There was a delayed fall of the blood sugar following the ingestion of carbohydrate giving a curve of the diabetic type. There was also a glycosuria without any rise of fasting or maximum blood sugar levels. This suggests that ACTH causes both a metabolic and renal diabetes. Blood glutathione levels were too variable for conclusions to be drawn.

N. Taylor.


In a very detailed paper, the authors have studied the metabolic effects of varying doses of an electrophoretically pure ACTH protein in a male patient suffering from rheumatoid arthritis. There was a clear difference between the effects of a small daily dose of ACTH (3-6 mg) which affected the salt and water metabolism, and larger doses (up to 50 mg) which affected carbohydrate metabolism and protein-carbohydrate metabolism as well. This is a valuable paper which should be read in its entirety by those interested.

N. Taylor.


This is a report on treatment by prednisolone and prednisolone acetate of 64 cases of chronic rheumatoid arthritis with marked anatomical and functional disablement. The definition, classification, and degree of response were estimated according to the standards of Steinbrocker (J. Amer. med. Ass., 1949, 140, 659).

The advantages of administration by the oral route were considered, and no secondary or physiological side effects of this steroid were found. A placebo controlled treatment was administered for the first 2 weeks, during which only three patients reported mild improvement. After therapy the improvement was evident in 2 weeks and increased as medication was maintained. Major improvement occurred in 24 patients (36 per cent.), eleven...
of whom had been moderately or totally incapacitated initially. The average length of treatment was 12-3 weeks. In half the cases the sedimentation rate returned to normal, and there was a decrease of 28 per cent. in the average level of eosinophiles. 26 patients (41 per cent.) showed improvement of lesser degree, eleven of whom had been seriously incapacitated in the first place. The third group of fourteen patients (21 per cent.) showed no improvement; these showed much less change in the sedimentation rate and none in the eosinophile level. Thus the greater improvement occurred with the less severe cases of initial anatomical and functional disability, and in the younger age group (20-39 years). Maintenance of improvement after cessation of therapy was assessed in eighteen cases showing major improvement, and it was evident that the longer the treatment the longer the improvement was maintained. Some cases given control tablets showed no significant difference in comparison with those who received nothing after the cessation of successful therapy, and this was considered to obviate psychological factors. The optimal dosage was considered to be 500 mg. daily for at least 8 weeks, the minimum average daily maintenance dose being 400 mg.

The authors conclude that "pregnenolone can be regarded as an aid in the treatment of rheumatoid arthritis, is less expensive than ACTH or cortisone, is easier for the patient, and has no secondary effects".

H. Coke.


Twenty-five patients with rheumatoid arthritis and eight with other diseases were given pregnenolone, either orally or intramuscularly, or by both routes. Dosage varied from 300 to 1,000 mg. daily. The patients were observed for an average of 14 weeks; two with rheumatoid arthritis improved and four had slight questionable improvement, but in all others no significant benefits were obtained. Two patients developed headache, which disappeared with reduction of dosage. After the use of intramuscular administration, painful local induration occurred regularly; sterile abscesses formed, requiring drainage, in two cases.---[Authors' summary.]


The scarcity of cortisone and ACTH, together with the reports of untoward side-effects following their prolonged administration, has stimulated investigation of a large number of steroids which might be thought to have somewhat similar properties. On the assumption that the beneficial effect of cortisone in arthritis may lie in the power of inhibiting connective-tissue proliferation, the authors have used the folic acid antagonist 4-aminopteroylglutamic acid (aminopterin) in the treatment of seven cases of rheumatoid arthritis, and one of rheumatic fever. The daily dosage employed was 1 to 2 mg., the total ranging from a minimum of 6 mg. to 40 mg. over periods varying from 6 to 21 days. It was found that although aminopterin has no analgæic effect it produced significant clinical amelioration in seven of the eight cases treated. There was no evidence, however, of any effect upon the course of the disease as indicated by the erythrocyte sedimentation rate, serum protein level, or leucocyte changes. As is often the case also with cortisone therapy, withdrawal symptoms in the form of acute exacerbation of the arthritic process for several weeks occurred.

It was not thought that the clinical effect of aminopterin is mediated through the pituitary or adrenal routes, but that it is due to direct inhibition of mesenchyme and, to a lesser extent, epithelial tissues. The toxic effects of aminopterin unfortunately appear to place a limitation on its practical use as a therapeutic agent.

W. S. C. Copeman.


The effect of single doses of sodium salicylate and sodium gentisate on the circulating eosinophils has been studied in normal healthy subjects. No significant depression was observed with plasma-salicylate concentrations up to 38 mg. per 100 ml. and plasma-gentiisate concentrations up to 35 mg. per 100 ml.---[Authors' summary.]


Combined treatment was given to 23 patients suffering from rheumatoid arthritis. There were no controls. Of the sixteen patients who received more than two treatments, nine reported definite improvement within a few days.

D. P. Nicholson.


The effects of the combined administration of deoxycorticosterone acetate and ascorbic acid to mice were studied by means of the cold test, egg-white reaction, and formaldehyde-induced arthritis. It is concluded from the results of these experiments that this combined administration has no cortisone-like activity. It showed no effect in protecting mice against formaldehyde-induced arthritis, in contrast to the previously reported work of Brownlee.

D. P. Nicholson.


This is a preliminary report on the study of the effect of acetylsalicylic steroids in eight patients suffering from "collagen" diseases—rheumatic fever, rheumatoid arthritis, ankylosing spondylitis, and fibrositis with endarteritis. Before treatment all patients had a low output of reducing steroids. With salicylates excretion was markedly raised, but fell at once on cessation of treatment. An increased output of reducing steroids was associated with clinical improvement. No regular variation was found in the excretion of 17-ketosteroids
during salicylate therapy, and variations in excretion were not correlated with the clinical course. The results suggest a relation between salicylate and cortisone therapy.

H. F. Turney.


In view of the traditional belief that chorea is a manifestation of rheumatic fever, cortisone was administered by these observers to two children suffering from acute chorea. In neither case was there any favourable response. The total amount of cortisone administered was 0.975 g. over a 14-day period in one case, and 2.175 g. over a 20-day period in the other. In one of these cases nearly 1 g. adrenocorticotropon was given later over a period of nine days, and this was also without significant effect upon the course of the disease.

W. S. C. Copeman.


Details are given of the treatment with adrenocorticotropon (ACTH) and cortisone of fifteen children with acute rheumatic fever. In most cases ACTH was used initially, since it was considered to act more rapidly than cortisone. Administration of the hormone was continued for 3 to 6 weeks in dosages varying with the potency of the preparation. One patient died and the first five had such small doses that the effects of treatment could not be assessed accurately. In the other cases there was a rapid regression of general signs and symptoms. Pericarditis subsided rapidly and there appeared to be definite though slower improvement in cases of myocardial or endocardial involvement. Established valvular lesions were unaffected. Some complications occurred, of which oedema and oliguria were the most serious. Relapses occurred when treatment was stopped suddenly or too early.

From a careful study of these cases the authors conclude that ACTH and cortisone have beneficial effects on the cardiac lesions in the acute stage of rheumatic fever but recommend further prolonged and statistical investigations to determine whether permanent cardiac damage is preventable by early hormone therapy.

Kathleen M. Lawther.


The clinical effect of pituitary adrenocorticotropon hormone (ACTH) has been observed in twenty patients with active rheumatic fever. In many patients the rheumatic process was severe, and most of them had active carditis. The initial response of fever and joint involvement was especially impressive, but pericarditis, subcutaneous nodules and other rheumatic manifestations also frequently disappeared during hormone therapy. Withdrawal reactions with clinical manifestations of rheumatic fever or with only elevation of the sedimentation rate were sometimes observed when hormone therapy was completed. In most but not all such instances these signs of rheumatic activity again subsided spontaneously over varying periods of time without any further treatment.

Of two patients with chorea, one showed striking improvement in association with pituitary adrenocorticotropon hormone therapy; the other failed to respond to a 10-day period of treatment with the hormone in large doses. Treatment has been completed in seventeen of the eighteen patients with rheumatic manifestations other than chorea. Three of these cases must be considered therapeutic failures. Although the total duration of active rheumatic fever varied greatly in the remaining fourteen patients, it was our impression that, on the whole, recovery took place sooner than it would have without treatment.

The apparent response of pericarditis congestive failure and subcutaneous nodules to pituitary adrenocorticotropon hormone in a number of patients and the complete disappearance in two patients of all significant murmurs strongly suggest that in some instances active carditis may be favourably influenced by hormone treatment. Also, there are hopeful indications that if therapy is begun early in an attack of rheumatic fever cardiac damage may be lessened or prevented.

The only harmful reactions definitely attributable to pituitary adrenocorticotropon hormone in this series were retention of fluids with aggravation of congestive heart failure and, in one instance, serious mental depression. It is possible that in one patient with longstanding, low-grade rheumatic fever the degree of rheumatic activity was greater after discontinuation than before the administration of the hormone. One instance of fatal jugular thrombophlebitis was encountered but as yet there is no definite reason to attribute this complication to pituitary adrenocorticosterone hormone therapy.

The mechanism of hormonal influences in rheumatic fever is not yet understood.—[Authors' summary.]


This is a report of the trial of adrenocorticotropon hormone (ACTH) in eleven consecutive cases of acute rheumatic carditis, in patients aged 6 to 18 years. Compared with previous experience ACTH had a notable effect on the course, duration, and resultant state. From their experience the authors suggest that the rheumatic process is reversible. Dosage used was 80 to 100 mg. every 6 hours for 3 days, and then 40 to 60 mg. daily for 4 days. Insufficient dosage may result in a relapse after cessation of treatment. Signs and symptoms of carditis subsided in 3 to 7 days, and patients were ambulant in 2 to 4 weeks.

David Nicholson.


This report summarizes in general terms the experience of the authors in the treatment of 64 cases of the "classic clinical picture of generalized rheumatoid arthritis"; 31 patients were treated with large doses of testosterone.
propionate. 28 patients with deoxy corticosterone (deoxy corticosterone) acetate and ascobic acid by the technique of Lewin and Wassern, and five patients with "artisone" (21-acetoxy-5-pregnenolone). Tables of results are given. The authors conclude that none of these three individual methods produced any specific beneficial effect. Assessment was based in general terms on subjective changes, and objectively on measurement of erythrocyte sedimentation rate and studies of blood. Controls were included. Subjective systemic improvement as a result of testosterone therapy was the only benefit noted in 61 per cent. of this group. Three patients given artisone were subsequently treated with adrenocorticotropic (ACTH) with the usual beneficial results.

Harry Cke.

The Synergistic Action of para Aminobenzoic Acid and Cortisone in the Treatment of Rheumatoid Arthritis. WIESEL, L. L., BARRITT, A. D., and STUMPE, W. M. (1950). Brooklyn Hosp. J., 8, 148. 11 refs. The authors treated three cases of severe or moderately severe rheumatoid arthritis with cortisone, the efficacy of the treatment being judged by assessment of joint pain and swelling. Cortisone was given in dosage sufficient to reduce these to a minimum. Reduction of the dose of cortisone to 25 mg. daily produced a relapse in all three cases. When, however, a daily dose of 12 g. sodium p-aminobenzoate was added to this small dose of cortisone, joint pain and swelling abated once more. Control treatment with p-aminobenzoic acid alone had no effect on the arthritis. G. Loewi.

Oral Use of Cortisone Acetate. BOLAND, E. W., and HEADLEY, N. E. (1951). J. Amer. med. Ass., 145, 8. 10 refs. It has been reported in several recent papers that cortisone can be given by mouth and will, in most cases, produce results in rheumatoid arthritis as striking as those obtained by intramuscular injection. It is also generally agreed that the dosage needed by the former route approximates to that usually given by the latter.

A report is given of the treatment of 23 patients with chronic rheumatoid arthritis by oral administration of cortisone, the study being designed to compare its effectiveness with that of intramuscular administration.

In all but one of these cases the oral route was found to be highly effective in suppressing the activity of the disease and controlling the rheumatic manifestations. It seemed in general that the therapeutic effects produced by oral administration occurred more rapidly and disappeared more rapidly than was the case when injections were used. In about half of the series larger amounts were needed to produce equal maintenance effects, the oral dose ranging from one-fifth to one-third more than the injected dose. No gastro-intestinal symptoms occurred as a result of oral administration, but the period of observation in the series was too short for any conclusions to be drawn as regards the safety of prolonged administration.

W. S. C. Copeman.


An analysis is presented of the results of treating seventeen men and 47 women suffering from rheumatoid arthritis with large doses (500 mg. daily) of pregnenolone by mouth. Placebo treatment was first given for 2 weeks, and three patients who improved during this period were excluded from the series. Of the remainder, 24 (38 per cent.) showed major improvement as evidenced by diminution of pain, increase in joint mobility, decrease in swelling, and increase in strength. Duration of treatment was from 3 to 30 weeks, with a mean of 12.3 weeks. In half the cases the erythrocyte sedimentation rate (E.S.R.) fell to normal, the mean figure after treatment being 64 per cent. of the original value. The average fall in eosinophil count in this group was 28 per cent. In 26 cases (42 per cent.) there was wild and less striking improvement. Fall in E.S.R. was less, the mean value after treatment being 74 per cent. of the pre-treatment level. Eosinophil count did not fall in this group. No improvement as regards either symptoms or E.S.R. occurred in fourteen cases. Relapse was usual after cessation of treatment. The authors believe that maximum improvement was obtained with 500 mg. daily; larger doses brought no further improvement. No constant untoward effects were noted. Oral medication is considered preferable to injection. Injected crystals may remain for weeks undissolved in the muscles.

C. L. Cope.


A survey of the literature on adrenocorticotropic stimulated the authors to give to 27 patients with rheumatoid arthritis or with osteo-arthritis one of three kinds of treatment: production of artificial pyrexia by stock vaccine or administration of deoxy cortione or progesterone, the last two being combined with ascorbic acid administration. Pyrexia produced a fall of eosinophil count and a corresponding increase in the ratio of uric acid to creatinine in the urine of three patients out of a group of ten. The second form of treatment, given in twelve cases, produced a fall in eosinophil count in two and a rise in the ratio of uric acid to creatinine in eight. Progesterone (one dose of 100 mg.) was given to only four patients, but clinical changes were not significant. Perhaps the changes observed are due to stimulation of both the pituitary and the adrenal glands.

E. Neumark.


Three short studies were made of seven cases, in women, of acute disseminated lupus erythematosus treated with cortisone and adrenocorticotropic (ACTH). The symptoms improved strikingly and rapidly, though high doses of cortisone (200 mg. daily) had sometimes to be used. The usual dose was 100 mg. daily. Relapse occurred at varying intervals after stopping treatment. Laboratory findings were either only slightly improved or were unchanged by the treatment. Wound healing was unaffected. The patients were euphoric during treatment and sometimes became temporarily unbalanced emotionally. Cessation of treatment was sometimes
followed by feelings of depression and weakness. Rounding of the face, acne, and hirsuties disappeared after cessation of treatment; strict perspiration. Salt and water retention was marked and, in one case, led to fatal oedema. Signs of a supervening acute infection could be dangerously masked. Cortisone and ACTH are dangerous substances, which should be used only in the presence of facilities for full laboratory control.

E. Lipman Cohen.


The authors record the occurrence of epileptiform convulsions in a patient with chronic asthma under treatment with cortisone. Cortisone was administered intramuscularly in 50-mg. doses, two being given on the first day of treatment and four (50 mg. 6-hourly) on subsequent days. The asthma began to improve on the 4th day and from that time the patient remained free from respiratory symptoms. On the 11th day of treatment he complained of headache which persisted during the next day, when he had four epileptiform fits. No cortisone was given on that day but 50 mg. was adminis-
tered the next day, and 100 mg. subsequently without fits recurring. An electroencephalogram (EEG) taken two days after the fits showed some rhythmic slow activity with no focal abnormality. A month later, when the dose of cortisone was being gradually decreased and the patient was receiving 50 mg. daily, lid-lag and tremor of the hands were observed; these symptoms disappeared and the asthma recurred 3 weeks after cortisone was stopped. The EEG was normal 3 months later.

Epileptiform seizures have previously been described as occurring during adrenocorticotropic hormone therapy but not during treatment with cortisone. The fits were attributed to cortisone because the patient had never previously had convulsions and there was no family history of epilepsy. During the 10 days before the fits occurred the patient had gained 5 lb. (2.26 kg.) in weight; the authors suggest that this was due to retention of salt and water and may have been responsible for the seizures.

R. S. Bruce Pearson.


The case is reported of a girl aged 13 years suffering from her third attack of rheumatic fever with cardiac involvement and a temperature of 104° F. (40° C.). She was treated with aspirin in doses up to 5 g. daily. During treatment her face became rounded and "puffy" but not oedematous, acne appeared on the forehead, chest, shoulders, and back, and she became morose. The urine contained a reducing sugar and there was a mild diabetic type of blood sugar tolerance. Water and chlorides were retained and there was a negative nitrogen balance. The albumin-globulin ratio returned to normal from its original reversed state and plasma fibrinogen level also fell to normal.

The authors regard these symptoms as manifestations of mild Cushing's syndrome which gradually subsided as the aspirin dosage was reduced. They consider them to be the result of aspirin treatment, compare them with the similar results obtained with cortisone, and discuss possible modes of action.

A. C. Crooke.


It is fortunate, in the opinion of the authors, that many disease processes can be favourably influenced without much knowledge of their aetiology. In this connexion they make a brief reference to the dramatic effects of cortisone and adrenocorticotrophin (ACTH) in rheumatoid arthritis, as demonstrated by Hench and his collaborators; they also refer to the work of Klemperer and others on the "collagen diseases" and to Selye's theory of "diseases of adaptation". Antigen-antibody reaction in the tissues is discussed, as well as the possible precipitation in the ground substance of "mucopoly-
saccharide acid". Some workers have claimed that cortisone and ACTH increase the amount of circulating γ-globulin and antibodies, while others have been unable to confirm these results; there is general agreement, however, that these hormones decrease the number of circulating eosinophils.

Cortisone and ACTH are difficult to produce and their prolonged use may result in unpleasant side-effects. The authors were encoureged in their decision to use nitrogen mustard (HN\[^4\]) by the fact that these drugs produce an eosinopenia comparable to that caused by the above hormones; their over-all effect was to produce all the phenomena of the "alarm reaction". Although extirpation of the adrenals does not abolish this reaction, hypoforthype of these glands (stimulation by nitrogen mustard) can be demonstrated at necropsy. The excretion of 17-ketosteroids in the urine is increased. Brief histories are given of fourteen cases of rheumatoid arthritis treated with HN\[^4\] intravenously (0-1 mg. per kg. body weight, on alternate days, to a total of four or five injections). Although these cases were of long standing with severe manifestations, the beneficial effects were not in doubt; in nine of them they were remarkable. Swelling and effusions largely disappeared and the power of locomotion was restored to bedridden patients. One month later, all cases were reassessed. In only three of them was there partial relapse; in the rest improvement was maintained. Blood counts showed a constant fall in circulating leucocytes, mainly in lymphocytes and eosinophils; leucopenia tended to increase a fortnight after cessation of treatment and reached its peak in these cases given more than 15 mg., thrombocytopenia frequently appearing in these cases. Although, in general, side-effects were not alarming, the authors consider it wiser to limit the number of injections to three (4 to 5 mg. each); with this dosage no complications need be feared. The erythrocyte sedimentation rate was unaffected by the excretion of uric acid in the urine fell at first but sub-
sequently rose, and that of 17-ketosteroids was initially increased and later returned to its original level.

Six cases of bronchial asthma have been treated so far (five of them in status asthmaticus). The effects were comparable to those reported from the use of ACTH and clinical improvement appeared to keep step with the reduction in circulating eosinophils. The authors have begun to treat other cases of "dysreaction" (dermatitis, myositis, scleroderma, psoriasis), but results are not yet available. Though the mode of action of HN\[^4\] is still...

Obscure they think that it is similar to that of ACTH and cortisone; they draw attention to the anti-mitotic effect of ACTH and HN².

D. Preiskel.


Having confirmed the fact that in sensitized animals treated with adrenocorticotrophin (ACTH) the incidence of cardiovascular lesions decreased, the authors describe a similar experiment. Rabbits were treated with cortisone and sensitized by intravenous horse serum. Among many interesting observations it was found that cortisone had little effect either on skin sensitization or on serum antibody levels. The incidence of cardiovascular lesions was much lower in the treated animals, the figures being practically identical with those obtained in a similar experiment with ACTH. The proliferative glomerular lesion died during treatment in spite of completely absent but a haemorrhagic lesion with focal glomerular necrosis was observed in many instances. It resembled the change seen in cases of diabetes mellitus and lupus erythematosus, but it is noteworthy that it was never observed in the animals treated with ACTH. The spleen contained foci of extramedullary blood formation and the liver excess of glycogen.

G. J. Cunningham.


This is a report on the results of treatment of seventy patients suffering from various types of neoplastic disease with pituitary adrenocorticotropic hormone (ACTH) and cortisone acetate. Eight patients with chronic lymphatic leukaemia received 100 to 200 mg. ACTH or cortisone acetate per day for 18 days to 3 months. All patients showed appreciable shrinkage of large lymph nodes, liver, and spleen during treatment. Relapse occurred at varying intervals after treatment was stopped, and in some it occurred slowly in spite of continued treatment. Subsequent courses of treatment proved beneficial in six cases. Some patients showed a rise in haemoglobin value and erythrocyte count in the blood during treatment. In all patients there was a transitory rise in the leucocyte count followed by a fall to below pre-treatment levels. In no patient was there alteration in the differential count or improvement in the bone-marrow picture.

Six patients with lymphosarcoma received ACTH or cortisone daily for 9 to 52 days. Definite shrinkage of tumour masses was observed in all cases: four patients were in the terminal stages of the disease when treatment was begun. They died during treatment in spite of transient improvement in the local tumours. In some patients remissions lasted for 3 months after stopping treatment, and subsequent treatment failed to reveal any sign of refractoriness to the active substance.

Of thirty cases of acute leukaemia receiving one of the drugs, thirteen showed "a good clinical and hematomal remission" and eight did not respond. Monocytic leukaemia appears to be unaffected by these hormones. In acute myeloid or acute lymphatic leukaemia remissions were of short duration and refractoriness to treatment rapidly developed. Of six patients with Hodgkin's disease, four showed slight shrinkage of enlarged lymph nodes and spleen; lasting benefit was not obtained. A patient with plasma-cell myeloma obtained a marked clinical benefit from ACTH. The bone-marrow picture remained unaltered. When treatment was stopped there was recurrence of symptoms within 24 hours.

[This paper provides very few details of treatment. Thus it is not stated which patients received cortisone and which received ACTH, and nothing is said of the relative merits of these hormones in the treatment of the various forms of reticuloisis.] A. Brown.


Eosinophil counts were performed on blood and bone marrow of seven patients before and during either cortisone or ACTH therapy. At a time of marked diminution in the eosinophils of the peripheral blood, the eosinophilic cells of the bone marrow were not decreased.—[Authors' summary.]


It has been shown that normal pregnancy is associated with a rise in the excretion of glucocorticoids and 17-ketosteroids, an indication of increased maternal adrenal cortical activity. In this paper the authors describe the case of a woman with adrenal insufficiency who was under frequent observation at the Presbyterian Hospital, New York, during pregnancy. The course of an earlier successful pregnancy in the same patient has been reported previously (Knowlton et al., J. clin. Endocrinol., 1949, 9, 514). Satisfactory control of the adrenal disease during the earlier part of pregnancy was achieved by the implantation of deoxycortone acetate (DCA) pellets, together with administration of sodium chloride by mouth, and from the seventh months onwards 2 mg. DCA was injected daily. The patient was delivered, 19 days prematurely, of a healthy infant and during the 4 months following remained in satisfactory health. The output of gonadotrophin, oestrogen, and pregnanediol was normal throughout this pregnancy. From the sixth week onwards the 17-ketosteroid excretion was markedly increased (from 4-5 to 9-9 mg. daily compared to 1 mg. daily one year before the onset of pregnancy). During the week following delivery steroid excretion fell gradually, and thereafter it was characteristic of Addison's disease. The output of neutral reducing lipids was within the range found in normal pregnancy, an unexpected finding in a patient with adrenal insufficiency.

A marked fall in eosinophil count occurred in the pregnant patient on administration of adrenocorticotrophin (ACTH): 10 days post partum this test was completely negative, even with large doses of ACTH given on five successive days. This finding does not support the possibility of the presence of residual adrenal tissue capable of responding to the stimulus of pregnancy. The output of 17-ketosteroids of the new-born infant was too small to account for the increase in maternal excretion. Preliminary tests revealed ACTH-like activity in acetone-dried placental tissue from this case, suggesting that the
Clinical Trials of A.C.T.H. in Haemolytic Anemia. 


The authors have treated three cases of haemolytic anaemia with ACTH in a dose of 100 mg. daily for 10 days. ACTH rapidly controlled the haemolytic phenomena in one case of acquired haemolytic anaemia; the symptoms have not recurred, and the Coombs test was negative and an abnormal antibody no longer present 8 months after treatment was started, although both remained positive for some time after symptoms had completely ceased. In two cases of congenital haemolytic anaemia there was little or no response to the administration of ACTH in similar doses. The authors suggest that the control of haemolysis by ACTH in acquired haemolytic anaemia is not due to suppression of the production of abnormal antibodies. Janet Vaughan.


Commercial cortisone acetate suspension injected intracutaneously into rabbits in amounts ranging from 0·5 to 2·0 mg. produced increased capillary permeability at the site of injection. By injecting in a similar way comparable amounts of different cortical extracts or substances used for the suspension of these preparations the author had demonstrated that the increase in capillary permeability was due solely to the material used as the vehicle for the cortisone, probably some type of adrenocorticotrophic hormone (ACTH). Treatment with cortisone acetate, free from any adrenocortical or vehicle, failed to increase capillary permeability when suspended in saline. This effect on the capillaries may possibly help to elucidate the action of cortisone acetate suspension in arthritic conditions and this additional variable, the author believes, will have to be taken into account in a number of clinical studies. A. I. Suchet-Kaye.


This study was prompted by the observation of several thrombo-embolic complications, including two fatal cases of pulmonary embolism, in patients receiving cortisone or adrenocorticotrophic hormone (ACTH). One patient the venous clotting time was considerably shortened during the administration of cortisone or ACTH, and in four out of six cases the "heparin retarded" venous clotting time was similarly reduced. No consistently significant changes were found in the prothrombin time, blood content of fibrinogen B, or protamine titration. It is concluded that both ACTH and cortisone frequently produce a hypercoagulable state of the blood, the mechanism of which is unexplained. C. Bruce Perry.


Working at the London Hospital and using the polarographic method of determination, the authors have studied the 17-ketosteroid excretion of 235 patients with endocrine dysfunction. Group 1 consisted of patients with adrenal cortical hyperfunction, and virilism or obesity resembling that of Cushing's syndrome. Usually, but not invariably, an increase occurred in 17-ketosteroid output corresponding to the degree of virilism; simple hirsutism alone did not appear to be related to increased output. In conditions resembling Cushing's syndrome, however, there was no...
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relation between the severity of the disturbance and the 17-ketosteroid excretion. Group 2 consisted of patients suffering from cortical failure, in whom a decreased excretion of 17-ketosteroids would be expected. In seven verified cases of Addison's disease and in nine cases of primary pituitary failure a strikingly low output of 17-ketosteroid was observed (less than 3 mg. in 24 hours); in primary testicular failure there was a far less marked fall in 17-ketosteroid excretion.

In various miscellaneous endocrine disorders, dwarfism, pituitary tumours, and thyrotoxicosis, the androgen output could not be related to the clinical findings.

The authors point out that factors other than endocrine disturbances, such as age, chronic illness, malnutrition, and impairment of liver function influence the 17-ketosteroid excretion, thereby reducing its value as a diagnostic test. The test is reliable in adrenal failure, either primary or due to pituitary failure, and of some value as an indication of adrenal hyperfunction in cases of virilism; in other endocrine diseases no reliance can be placed upon it as a diagnostic aid. 

Nancy Gough


A case of acute glomerulonephritis was studied for 43 days. During this period, 200 mg. cortisone was administered daily for 12 days. The signs of nephritis at that time were haematuria, albuminuria, and the presence of urinary casts. While the patient was on cortisone there was a rise in temperature and increase in protein and erythrocytes in the urine, probably a non-specific effect. It was considered doubtful whether cortisone had been of benefit.

G. Loewi

Cortical Steroids in Treatment of Cancer. Observations 

The effect of pituitary adrenocorticophin (100 to 200 mg. daily for individual periods of 2 weeks to 3½ months) and of cortisone (100 to 300 mg. daily for similar periods) was studied in 26 cases of far advanced malignant disease. Most patients showed marked temporary improvement in general condition. The improved state lasted until side-effects from long-continued therapy ensued or complications produced by the progress of the neoplastic disease developed. The side-effects included disturbances of electrolyte balance (such as sodium retention or potassium loss), decrease in glucose tolerance, mental changes, altered response to infection, pigment disturbances, sexual disturbances, and development of Cushing's syndrome. Temporary regression of neoplastic lesions was observed in three cases of Hodgkin's disease, five cases of lymphosarcoma, and one case of chronic lymphatic leukaemia; a doubtful regression of angio-endothelioma (Ewing's sarcoma) occurred with ACTH. In cases of carcinoma, acute leukaemia, myelogenous leukaemia, and melanoma the disease was not controlled. Because of the physiological alterations produced by these hormones when given in large doses, however, repeated or prolonged therapy is ill-advised.

L. A. Elston


Cortisone was used in the treatment of twelve patients with muscular or neuromuscular disorders, thorough clinical, biochemical, and electromyographic investigations being carried out before, during, and after treatment. In all cases muscle biopsies were performed before cortisone was administered. Two typical cases of dystrophy myotonica were completely free of myotonia while they were having cortisone, this abnormality returning when cortisone therapy was stopped; there was also some increase of muscle power during treatment. Two patients with motor neurone disease showed no improvement with cortisone, while one patient with myasthenia gravis (apparently associated with a tumour of the thymus) became very much more myasthenic while he was having cortisone: when administration was stopped his condition gradually returned to its previous state. Of two patients with disseminated lupus erythematosus and marked muscle weakness both constitutional symptoms and muscle power improved with cortisone in one case, while in the other there was no increase of muscle power in spite of relief of the constitutional symptoms. One patient had an unusual type of muscular dystrophy with flexion contractures of the elbows and knees and fixation of the spines in hyperextension: no improvement occurred in this man. The remaining four patients suffered from a condition which the authors call "menopausal myopathy" in which, during the 50-60 age period, weakness of the muscles of the shoulder and pelvic girdles develops, with comparatively little wasting but with histological changes typical of a myopathy. In three of these patients there was considerable increase of power during cortisone administration and relapse when it was withdrawn. The authors have previously noted improvement in this condition when wheat germ oil is given and relapse when it is discontinued, and they raise the question as to whether "wheat germ may not contain building blocks for steroid hormones". J. W. Aldren Turner


This investigation was prompted by the work of Pincus and Hoagland, which suggests that in schizophrenia the adrenal cortex does not respond normally to stimulation by adrenocorticotropic hormone (ACTH), and that of Gildes and others, which suggests that the response is normal.

The effects of ACTH on adrenal cortical function, as measured by eosinophil counts, the urinary uric acid: creatinine ratio, 17-ketosteroid excretion, and sweat sodium concentration, was the same in psychotic patients as in normal persons. When, however, 100 g. dextrose was given 1 hour after a single injection of 25 mg. ACTH, there was a greater rise in the blood sugar level over a 3-hour period in psychotics than in normal persons. (It is admitted that the numbers studied were so small that chance may have dictated the difference found in the two groups.)

It is known that large doses of ACTH or cortisone may give rise to mental changes in persons previously normal
mentally. The authors report two cases, both patients being manic depressives, in which the condition deteriorated after administration, in one case of 570 mg. ACTH in 17 days, and in the other of 900 mg. in 10 days. The history is also recorded of five patients previously given insulin or electric convulsion therapy who showed evidence of lessened responsiveness to ACTH.

It is suggested, therefore, [on rather dubious evidence] that psychotic patients show exaggerated metabolic changes after administration of ACTH, and that it might be possible to relate psychosis to metabolic changes consequent on an unusual response of the adrenal cortex to ACTH, or of other tissues to cortical hormone released during ordinary stress. W. V. Wadsworth.


Intramuscular doses of adrenocorticotropic hormone (ACTH) and/or cortisone (5 mg. of each) were given to male Swiss mice weighing 10 to 14 g., and to male hamsters weighing 22 to 27 g., in groups of nine to 21 animals. The virus was maintained by serial intracerebral passage in mice and its identity checked periodically by neutralization tests with anti-Lansing monkey serum. The intracerebral inoculation dose for both animal species was 0.05 ml. of the brain emulsion, suitably diluted with saline. All surviving animals were examined daily for a period of one month.

Intracerebral inoculation of the virus in mice given cortisone and ACTH 2 hours previously was followed by a shortening of the incubation period and correspondingly earlier mortality compared with the controls. Intraperitoneal injection of the virus did not produce this effect.

In hamsters the effect was more striking. Previous experiments showed that these animals were normally quite resistant to intracerebral inoculation of poliomyelitis virus. After pretreatment with cortisone or ACTH and cortisone, what is known as a mild infection with small mortality rate became a rapidly progressing, violent, and uniformly fatal disease. ACTH alone failed to produce this effect, possibly, the author suggests, because of the elaboration of an unknown factor capable of reversing the enhancing effect of cortisone.

Norval Taylor.


It has been shown that adrenocortical extract (ACE) and cortisone will counteract the depressive effect of deoxycorticosterone acetate (DCA) on brain excitability in intact rats. The present report concerns the effects of ACE and cortisone on adrenalectomized rats after implantation of DCA. Adult male Sprague-Dawley rats were used and the "electroshock threshold" (EST) was determined by the technique described by Davenport (Amer. J. Physiol., 1949, 156, 322). Some of the rats were then subjected to adrenalectomy and six 15-mg pellets of DCA were implanted, some were left intact but DCA was implanted, and some served as untreated controls. The EST of the intact DCA-implanted rats increased in comparison with that of the controls, and that of the adrenalectomized DCA-implanted animals increased even more markedly. Both ACE and cortisone reduced the elevated EST of the adrenalectomized DCA-implanted rats; the degree of reduction was not, however, related to the loss of body weight. On withdrawal of the hormones the EST slowly increased to its original level.

These observations support the theory that DCA acts by antagonizing cortisone-like steroids at their site of action rather than by inhibiting pituitary release of adrenocorticotropic hormone (ACTH), since in the adrenalectomized animals the endogenous secretion of cortisone-like steroids was nil. The authors suggest that the chemically similar DCA and cortisone compete for the same strategic loci in the cell. The test animals responded more rapidly to cortisone and ACE treatment if given water to drink instead of sodium chloride solution, suggesting a relationship between EST and the extracellular sodium level.

The possibility that brain excitability determinations may be useful as a method of assaying cortisone-like compounds is being explored. Nancy Gough.


It has been shown that ingestion of glucose enhances the response of hypophysectomized animals to adrenocorticotropic hormone (ACTH), suggesting that the blood sugar level affects the action of ACTH on the adrenal cortex.

This paper records the results of a study of adrenal corticoid response to ACTH in hypophysectomized male rats under conditions of adrenaline-induced hyperglycaemia and insulin-induced hypoglycaemia. Determinations of blood glucose, adrenal cholesterol and ascorbic acid, plasma ascorbic acid, and liver glycogen concentrations were made by standard methods. ACTH was injected subcutaneously, followed by adrenaline and insulin at intervals of 60 and 90 minutes respectively, so that the full action of ACTH coincided with the maximum hyper- and hypo-glycaemic levels. Hypophysectomized rats receiving ACTH, insulin, or adrenaline alone were killed at corresponding time intervals for comparison.

Changes in blood sugar level induced by insulin or adrenaline were not influenced by ACTH administration. Moreover, neither adrenaline nor insulin modified the effect of ACTH on the liver glycogen and adrenal cholesterol and ascorbic acid levels. Hence hyperglycaemia per se does not enhance the action of ACTH on the adrenal cortex; the effect of alimentary hyperglycaemia must be attributed to an increase in the total store of carbohydrates or to an excess production of intermediary metabolites. Nancy Gough.


This is believed to be the first case report of irreversible damage to the fascicular zone of the adrenal cortex following treatment with cortisone and ACTH.

The patient was a negroess aged 36 who had had lupus.
erythematous and chronic cervicitis for 2 years. She was treated with radium for the cervicitis, but became progressively worse, with fever, malaise, weakness, and joint pains. She developed dry, scaly, depigmented areas on the nose, cheeks, and elsewhere, and there was stiffness and atrophy of the interosseous tissues of the hands and feet. All joints were painful on motion. The clinical diagnosis was lupus erythematous disseminated.

Cortisone was given in doses of 300 mg. on the first day, 200 mg. on the second day, and 100 mg. daily thereafter for 7 days. Soon after the start of treatment she felt much better and the joint pains had gone. A second course of cortisone was given, but pneumonitis developed and the patient died some 3 weeks later.

At necropsy the main findings were in the adrenal cortex. The cells of the zona fasciculata showed pyknosis of their nuclei and the cytoplasm was largely absent. As the lesions of lupus erythematous disseminated were relatively inconspicuous in comparison with the marked damage to the adrenal cortex, it was presumed that adrenal cortical failure was the cause of death.

**R. B. Lucas.**

**Role of Cortisone in Regulation of Inflammation.**


The authors describe their investigations into the histology of experimentally induced allergic and traumatic inflammation in adrenalectomized and adrenalectomized and cortisone-treated mice. Adrenal cortical secretions and exogenous cortisone were shown to inhibit inflammation without interfering with the antibody-antigen reaction. [As this paper is not readily abstracted, the original should be consulted for the technical details.]

**Norval Taylor.**


ACTH had no beneficial effect when given to a patient suffering from periarteritis nodosa and to four patients with severe psoriasis. Remarkable improvement in a man of 49 suffering from pemphigus was maintained 3 months after cessation of treatment, but a similar case in a female patient of 68 relapsed whenever the ACTH was withdrawn. There was marked improvement in one patient with diffuse scleroderma, but no improvement in a second case. Small doses (5 to 45 mg. daily) were given, and it is advised that the treatment should be withdrawn gradually. No serious side-effects were seen, but most patients complained of tiredness and apathy on withdrawal of the drug.

**John T. Ingram.**


The authors list nine skin conditions in which, according to published reports, pituitary adrenocorticotrophic hormone (ACTH) may be beneficial, and seven in which it appears to be ineffective or even detrimental. In the present paper they report the effects of ACTH treatment in eleven cases of bullous dermatosis of various types seen at the Columbia-Presbyterian Medical Center, New York.

In five cases of pemphigus vulgaris, ACTH therapy was instituted after the disease had been present for periods ranging from one week in one case to one year in another. The first course usually consisted of 60 to 100 mg. daily for 3 to 20 days, and in every case produced a remission, which was sometimes dramatic; but relapses always occurred on withdrawing the ACTH and the condition responded less well and only to greatly increased dosage in subsequent courses until finally new lesions appeared in spite of continued therapy. One of these patients died of fulminating pemphigus and another of mesenteric thrombosis, which was possibly due to co-existing Buergers’ disease or to the effect of ACTH itself.

Two patients with pemphigus vegetans were also treated, both patients undergoing great clinical improvement and being discharged on a maintenance dose of about 100 mg. ACTH a day; one of them has actually returned to work. Of two cases of erythema multiforme pemphigoides, temporary clinical cure was obtained in one with an 11-day course of 100 mg. ACTH daily, followed after 6 months by a course of weekly injections of 50 mg. cortisone acetate. The other patient, after initial improvement on a dose of 80 mg. ACTH daily, decreasing to 40 mg. daily, relapsed 5 weeks after stopping the treatment, but again responded well to 40 mg. ACTH daily for 14 days. He has since been lost sight of. (In these two cases there was some difference of opinion concerning the diagnosis.) Two patients with epidermolysis bullosa of the congenital dystrophic type showed no objective improvement on treatment with cortisone acetate although appetite and sense of well-being improved.

In all eleven cases the blood pressure was initially low (96 to 108 mm. Hg systolic) but rose to normal levels on treatment. The frequent association with pemphigus of degenerative or necrotic lesions of the adrenal cortex and disturbances of serum electrolyte content is pointed out, although only in four of the present series was any abnormality of the blood chemistry, in the form of sodium or diminished serum sodium content, found. ACTH and cortisone appear to produce identical effects, namely, easier management of the case, restoration of serum electrolyte balance, improvement of systolic blood-pressure and gain in weight.

**Ferdinand Hillman.**


Female rats treated with electrophoretically pure somatotrophic hormone (STH) develop polyuria and hypertension with nephrosclerosis, myocarditis, and pancreatic polyarteritis nodosa. The liability of the animals to these toxic effects is augmented by unilateral nephrectomy and an excessive intake of sodium chloride. The toxic effects are similar to those produced previously by treatment with high doses of deoxycortone acetate (DCA) or a mixed anterior pituitary hormone preparation (LAP) which is rich in growth factor. They can be prevented by giving cortisone simultaneously in big enough doses to produce adrenal cortical atrophy. STH also increases the liability of rats to experimental
arthritis, while simultaneous administration of cortisone inhibits it, but larger doses of cortisone are required to prevent arthritis in STH-treated than in untreated rats.

It is suggested that STH stimulates the production of mineralo-corticoids like DCA by the adrenal cortex and also sensitizes the peripheral tissues to DCA-like substances. STH appears to be as important as ACTH in the production of the "diseases of adaptation". It is responsible for the activity of the mineralocorticoids which stimulate defensive granuloma formation, while ACTH is responsible for the activity of the glucocorticoids which inhibit such defensive mechanisms.

A. C. Crooke.


In a 35-year-old married woman who was "an example of a typical personality type" such as has been described in patients with chronic ulcerative colitis, the colitis, pyrexia, and general condition steadily worsened in spite of intensive therapy, including the administration of antibiotics. Upon the administration of cortisone, in doses of 100 mg. every 8 hours on the first day, 100 mg. every 12 hours on the second day, and 100 mg. daily for the next 10 days, a striking improvement in "responsiveness, affect, and mood" was observed as from the third day; this was followed, as from the eighth day, by satisfactory improvement in the diarrhea, pyrexia, and vital signs and proctoscopic appearance of the colon. Improvement was maintained after the cortisone was discontinued, and the remission was still complete after 6 months.

The point of this report is that "the beneficial response was first manifested in the personality." [It should be noted, however, that "the possibility of a miraculous remission was suggested to the patient" before treatment.]

Joseph Parness.


In five patients suffering from diarrhea, pyrexia, and the usual toxic manifestations of an acute exacerbation of chronic ulcerative colitis the usual measures, including the administration of antibiotics, had given no response. Upon the administration of ACTH in doses of 25 mg. every 6 hours for 10 days a fall in temperature to normal occurred in three patients, but without improvement in diarrhea or in the appearance of the rectal mucosa; in one case the subsidence of the temperature to normal was accompanied by improvement in the diarrhea and in the appearance of the rectal mucosa; in one patient (who had a low-grade pyrexia) there was no reduction of temperature, nor was there improvement in diarrhea or in appearance of rectal mucosa.

ACTH appears to be effective in reducing the febrile reaction in acute toxic ulcerative colitis. Joseph Parness.

ANNALS OF THE RHEUMATIC DISEASES


In a large series of patients subjected to equal physiological adrenal cortical stimulation with ACTH should inhibit or reverse all of the physiological phenomena produced by sudden severe stimuli. When this does not happen, the author suggests, the normal response is not sufficient in relation to the intensity of the stimulus. Extensive burns which, if involving over 60 per cent. of the body surface, are usually fatal, provide such a stimulus.

To test this theory a case of petrol burns involving over 70 per cent. of the body surface was treated, after 24 hours of the usual routine burns treatment, with ACTH alone, 20 mg. being given 6-hourly intramuscularly; this was gradually reduced to 10 mg. 6-hourly by the 32nd day and was continued at this dosage until the 92nd day when it was discontinued. On this treatment the patient improved rapidly, showing minimal signs of toxicity and prostration and experiencing very little pain. Kidney function, increased early and chloride excretion remained low. Haemoconcentration did not occur, and the anaemia which was present was attributable in part to haemodilution. Mild hypoproteinaemia was recorded.

No fibroblastic proliferation was noted, and epithelization was rapid except in the areas of very severe third-degree burns. Here 29 out of thirty homologous pinch grafts from two donors took when applied on the 42nd day and epithelization was complete by the 101st day. Some fibroblastic proliferation occurred after cessation of the drug and melanin deposits were extremely intense especially at the belt line.

The author considers that the tremendous saving both in expense and personnel calls for a re-evaluation of present methods of treating such patients, and that the success of pinch grafting may open up new fields for transplantation and plastic surgery.

A. Akroyd.


The authors review the literature and give an account of their own experiments on three rabbits. Previous workers have shown that in rabbits and mice ACTH or cortisone retards the growth of all elements of connective tissue, as well as the growth of granulation tissue in open wounds in fracture. These effects are not blocked by ascorbic acid. After cortisone injection there was no change in the macroscopical appearance of healing, sutured skin incisions in rabbits, compared with similarly sutured incisions made in the same animals and allowed to heal before injections of cortisone were started.

Microscopical specimens (haematoxylin-eosin and Weigert elastin stains) showed marked differences in wound healing in the cortisone-injected series: fibroblastic proliferation, growth of capillary vessels, and union by epithelium they lagged behind the controls. There was a greater tendency to haemorrhage into the wounds, and atrophic changes of the skin remote from the wounds were demonstrated.

A possible clinical application—the use of cortisone to prevent the overgrowth of fibrous and granulation tissue and keloid formation—is mentioned.

W. Skyrme Rees.


In studying the effect of cortisone on the various manifestations of the nephrotic syndrome in eleven patients at Stanford University School of Medicine.
San Francisco, the sodium-retaining activity of the urinary corticoids, which is increased in the nephrotic syndrome, was measured by biopsy in adrenalectomized rats by comparison with the effect of a standard dose of deoxycorticene acetate. As might be expected, during cortisone administration (100 to 300 mg. a day for 5 to 16 days) some manifestations of the renal upset were made worse. Albuminuria and oedema tended to increase, sodium excretion diminished, and the serum protein level rose a little. In two cases a rise in serum potassium level prevented the completion of treatment. When cortisone was stopped, however, diuresis occurred, in six patients, with loss of all oedema. This improvement lasted from a few days to several months, usually starting 3 days after cortisone was stopped. There was also a reduction in the albuminuria and excretion of sodium-retaining corticoids. Creatinine excretion increased, as did the serum sodium level. There was no alteration in serum cholesterol level, haematocrit, or erythrocyte sedimentation rate. [The blood urea level is not mentioned.] The value of cortisone is thus apparent only after its withdrawal, during the time when endogenous adrenal activity is depressed. Experimentally, adrenalectomy will reduce albuminuria, and intercurrent infection is known to bring about clinical improvement in cases of wet nephritis. The other five patients were not improved, but the subsequent improvement of four of them following intravenous albumin therapy is reported, and these two forms of treatment may be complementary. The authors point out that the fundamental disorder in this disease still appears to lie in the kidney.

K. Gurling.


A preliminary report on the results of treatment with the first supplies of cortisone used in Dublin, including an account of the effects of the drug in both ocular and general disease. In the ocular cases, subconjunctival injection of 1-25 mg. at 5-to 6-day intervals was the usual dosage, although the effects of systemic administration were observed in some cases. Statistics were given, but it is stated that scleritis associated with severe arthritis has been seen to clear rapidly with systemic treatment, that keratitis, and particularly interstitial keratitis, has responded well, and that the cleaning of corneal opacities due to chemical burns has appeared to be accelerated. Absorption of keratic precipitates and clearing of the vitreous, with improvement of vision in iridocyclitis is also reported.

H. E. Hobbs.


The results of cortisone therapy in fourteen cases of phlyctenular kerato-conjunctivitis are described. In twelve of them dramatic resolution of the phlycten with whitening of the eyes was seen within 48 hours of treatment being begun. The remaining two cases, in which the exacerbation was of long duration, responded in four and six days respectively. In one instance of a minimal lesion, a single drop (of a 1 in 2 dilution of cortisone acetate) was sufficient, in three others, seen during the first attack, a single subconjunctival injection of 0.1 ml. was employed, and for the remaining (recurrent) lesions drops were instilled hourly for two days and q.i.d. for a short period. Similar results in eleven of a further twelve cases treated later are mentioned.

H. E. Hobbs.


The report of a case which presented with severe bilateral conjunctivitis, ulcerative stomatitis, and balanitis, accompanied by pyrexia and a dry cough. Initial treatment with aureomycin (250 mg. 4-hourly, orally, and a mouth wash containing 40 mg. per ml.) was followed by gradual improvement of the general condition, but the ocular and oral conditions persisted a week later and bullous cutaneous eruptions had appeared.

Parenteral cortisone (600 mg. in 3 days) produced a dramatic response within 24 hours, and no recurrence was seen during the succeeding 4 months. H. E. Hobbs.


An interstitial keratitis of five weeks' duration, in a 10-year-old girl, responded poorly to systemic penicillin. Then cortisone, 100 mg., was given daily. By the sixth day of treatment the corneas were clearing markedly; by the 14th day little haze was present. The old neglected lesion in the right eye cleared more completely than the fresh lesion in the left eye. There was no change in the blood Wassermann reaction. C. McCulloch.


The chief value of ACTH or cortisone is to prevent an acute ocular inflammation from becoming chronic. The only cases of iritis that did not respond to cortisone were those in which the pupil was fixed and not dilatable. Intramuscular ACTH is effective in some cases of chronic granulomatous uveitis. Subconjunctival injection of cortisone is effective in acute iritis, chronic keratitis, and helpful in vernal catarrh.

I. E. Gaynon.


The authors used topical and subconjunctival therapy in a series of thirteen cases with anterior segment eye disease—eight of iritis, two of episcleritis, and one each of conjunctivitis and blepharitis. Drops were mainly used consisting of 25 mg. per ml. stock solution of cortisone acetate diluted with an equal amount of normal saline and they were administered hourly. The immediate results were excellent, the late results were not discussed.

S. J. H. Miller.


The results of local cortisone treatment in a series of 53 patients are recorded. The author considers that cortisone administered in the form of drops is more effective than subconjunctival injection.

C. A. Cook.


Other General Articles


Addison’s disease occurring during adolescence in two brothers, and the necropsy findings in one of them, are reported.

The first patient, a boy of 12, had typical clinical and biochemical signs which became normal on treatment with adrenal cortical extract, deoxycortone acetate, and salt. Associated endocrine changes—bilateral undescended testicles and an underdeveloped penis—were rectified following the administration of chorionic gonadotrophin. His brother, aged 17, was admitted within a year; although the only abnormality was buccal and generalized pigmentation, he suddenly deteriorated after the administration of intravenous saline and died in 3 days. At necropsy both suprarenal cortices showed simple atrophy; the thymus was grossly enlarged, and both lungs had supernumerary lobes.

There was no family history of Addison’s disease. The authors consider that simple atrophy of the suprarenals was the cause of the disease in both brothers, although the younger one had lived on unboiled, unpasteurized farm milk all his life and had calcified abdominal lymph nodes; they point out that the occurrence of Addison’s disease at so early an age and in siblings suggests a genetic basis.

The literature on the genetic factor in Addison’s disease is briefly reviewed, but it is emphasized that most of the cases were inadequately documented. The present authors conclude that the evidence in favour of a genetic factor in Addison’s disease is suggestive. Helen Grant.


The author records sixteen cases of renal insufficiency, due to various lesions, in which skeletal changes were discovered. Two main osseous lesions were seen: (1) bony trabeculae coated with osteoid and showing a resemblance to rickets, and (2) bony destruction with fibrous-tissue replacement suggestive of osteitis fibrosa. Whereas the youngest children showed changes of rickets only, older cases presented a mixed picture of one of osteitis fibrosa only. Stress is [rightly] laid on the fact that the bony lesions which may complicate renal disease are exceedingly complex, and that while excess parathormone may or may not play a part, it is quite erroneous to regard these lesions as purely secondary to hyperparathyroidism and therefore unrelated to the rickets.

G. J. Cunningham


The authors report an investigation into the possible relationship between the serum cholesterol content and basal metabolic rate (B.M.R.) which was carried out at North-western University Medical School, Chicago, on 72 healthy male students between 19 and 27 years of age. The subjects were given a standardized supper and kept under a standard regimen during the evening before the tests, which were all carried out before breakfast. Two B.M.R. determinations were made with a Benedict-Roth apparatus, the average of two 6-minute runs being taken, followed by a blood serum cholesterol estimation, carried out in duplicate by a modified Bloor’s method. The whole procedure was repeated after a 7-day interval with 32 of the subjects, and after an average of 38 days with the remaining forty. The mean B.M.R. for the whole group was 37-0 calories per square metre per hour (range, 30-9 to 45-3) and the test-rest correlation coefficient for the two successive sessions was +0-60. The mean serum cholesterol value was 189 mg. per 100 ml. (range 131 to 303) and the test-rest correlation coefficient at 7- and 38-day intervals was +0-62, indicating that Bloor’s method was reliable and that the serum cholesterol level was a more stable characteristic of normal individuals than the basal metabolic rate. There was no correlation between the cholesterol value and the basal metabolic rate, as is shown by the statistically insignificance correlation coefficient of —0-60. R. P. Hullin.


During a recent smallpox epidemic in Djakarta some of the patients had affections of the joints. The author surveys the literature and reports the cases of three Indonesian children who had joint affection with smallpox: (1) Boy aged 21 months: left elbow swollen, radiographic changes in left elbow and right wrist, no puncture, Wassermann and Kahn reactions negative. (2) Girl aged 9 years: both elbows swollen, pus found but not investigated further, Wassermann and Kahn reactions strongly positive. (3) Girl aged 4 years: both elbows, both knees, right wrist, and left shoulder affected, pus found in elbows but not examined, Wassermann reaction negative and Kahn reaction ±.

[The diagnosis of polyarthritis variolosa is not proved. Although no exact figures are given there appear to have been something like seven cases with joint affections out of 2,500 smallpox cases, which rather indicates an intercurrent disease.] J. Agerholm.