ABSTRACTS

This section of the ANNALS is published in collaboration with the two abstracting Journals, ABSTRACTS OF WORLD MEDICINE, 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); Disk Syndrome; Gout; Pararheumatic (Collagen) Diseases; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section “ACTH, Cortisone, and other Steroids” includes abstracts and titles of articles dealing with research into the scope and modus operandi of steroid therapy.

Acute Rheumatism


It has frequently been suggested that those persons who are susceptible to rheumatic fever have an intrinsic factor unduly sensitizing them to Group-A streptococcal infections of the upper respiratory tract. At the Canadian Red Cross Hospital, Taplow, Buckinghamshire, they therefore investigated the relation between the incidence of rheumatic fever and the presence of blood-group antigens (A, B, H, and Lewis) in the saliva and, presumably, the mucous secretions of the throat. Saliva obtained was prepared and titrated against Lewis' antisera from immunized rabbits, a heavy white precipitate after one hour's incubation indicating a positive reaction. The reliability of the test was confirmed on saliva from healthy people of known Lewis blood group. The precipitin test for Lewis' substance and the haemagglutination-inhibition test for A and B substances were also carried out with saliva from 115 healthy subjects. Analysis of the results and those of previous workers showed that 3.75 per cent. of patients did not secrete A, B, H, or Lewis antigen.

Altogether 450 patients with rheumatic fever, 253 with rheumatoid arthritis, and 460 healthy school-children were studied, the precipitin and/or haemagglutination-inhibition tests being carried out in the cases of rheumatic fever and the precipitin test only in the other two groups. Lewis' positive results were obtained in 100 (21.7 per cent.) of the healthy controls, fifty (19.8 per cent.) of the patients with rheumatoid arthritis, and 124 (27.6 per cent.) of those with rheumatic fever. When allowance was made for the 3.75 per cent. total non-secretors, the incidence of Lewis-antigen secretors in the healthy controls was 22.6 per cent., in the patients with rheumatoid arthritis 20.6 per cent., and in those with rheumatic fever 28.7 per cent. This difference was significant at the 5 per cent. level.

As secretor status is genetically determined, the authors state that these figures support the view that there is an hereditary factor in rheumatic fever. They postulate the possibility of a blood-group linked haptenic material being present in the throat secretions during a streptococcal infection before the onset of rheumatic fever, the hapten being absorbed on the bacteria and becoming completely antigenic.

M. Kendal.


The authors of the first article, working at the Institute of Therapeutics of the Academy of Medical Sciences, Moscow, have studied hyaluronidase activity in the serum in cases of rheumatic fever in relation to the severity of the disease, and the response to treatment. They employed McClean's method of estimating hyaluronidase. Although they could not establish any direct relationship between the hyaluronidase content of the serum and the severity of the case, its presence in quantities above the "normal" level was constantly associated with clinically active rheumatic fever and the titre diminished in parallel with clinical improvement.

The author of the second article, on the other hand, has estimated antihyaluronidase activity in the serum of fifty patients with active rheumatic fever at the First Moscow (Order of Lenin) Medical Institute, and comes to the following conclusions:

(1) During rheumatic fever there is an increased concentration in the serum of anti-hyaluronidase and of the "non-specific" hyaluronidase inhibitor;

(2) The inhibiting activity of the serum rises with aggravation of the disease, indicating a parallel
rise in the hyaluronidase content; its measurement may be of use for diagnostic and prognostic purposes;

(3) The administration of antirheumatic remedies such as salicylates, ACTH, and "butadion" (a derivative of phenylbutazone) brings about a fall in the titre of antihyaluronidase and of non-specific inhibitors concomitantly with the diminution in hyaluronidase activity;

(4) In rheumatic fever the balance of the hyaluronic-acid--hyaluronidase system is changed and the increase in enzyme activity causes destruction of mucopolysaccharides, one of the most important constituents of connective tissue. The antirheumatic remedies restore the enzyme system to normal and diminish the destruction of mucopolysaccharides. A. Koby.


The authors have studied, at the Hôpital Edouard-Herriot, Lyons, the changes occurring in the bone marrow in 100 children with rheumatic fever at various stages of its evolution, and also in young patients with chorea (22 cases), scarlatina (16), acute nephritis (28), and other conditions (25). In order that the procedure should be as little upsetting to the child as possible, they puncture a spinous process, or in some cases the anterior superior iliac spine, under local analgesia (2 per cent. lignocaine). Several films of the marrow are studied, analysis being made of not less than 1,000 cells.

The general conclusion is that the myelogram is of definite diagnostic value in atypical forms of rheumatic fever. The characteristic change is an increase in the number of plasmocytes; the average proportion of nucleated cells in the acute phase of rheumatic fever was 5-4 per cent. (range 2-3 to 15), the normal value being taken as 0-4 per cent. Lymphocytes also showed a definite increase, but the proportions of neutrophil and eosinophil granulocytes were normal. In 33 cases a second myelogram was obtained some 2 to 4 weeks after the first, and a third myelogram in eleven of these, so that the effect of cortisone treatment could be observed. All the cases showed some reduction in the number of plasmocytes, but in the majority the figure did not fall to normal.

Similar changes were observed in the cases of chorea and scarlatina, and also in certain cases of acute nephritis in which there was evidence that a haemolytic streptococcus was concerned. A striking feature of the myelogram in scarlatina was an intense eosinophilia, as well as a marked plasmacytosis clearly distinguishing it from rheumatic fever. Kenneth Stone.


Correlation between the Clinical Diagnosis and the Findings at Routine Roentgenological Examination of the Heart in Rheumatic Valvular Disease. [In English.] Aubert, A. B., and Amundsen, P. (1956). *Acta med. scand.*, 156, Suppl. 319, p. 54. 10 refs.


Rheumatic Fever in Norway 1930-1952. (A) Mortality from Rheumatic Heart Disease between the ages of 5 and 49 Years. [In English.] HANSEN, P. (1956). *Acta med. scand.*, 156, Suppl. 319, p. 47. 8 refs.


Chronic Articular Rheumatism

(Rheumatoid Arthritis)


Writing from the Stalin Second Institute of Medicine, Moscow, the author states that rheumatoid arthritis shows no preference for patients of a specific nervous constitution. The various types of nervous constitution considered in the paper are classified mainly according to the ideas of Pavlov and are referred to as different types of "higher nervous activity".

In the course of the disease marked changes occur in the higher nervous activity, which are manifested mainly by a weakening of the inhibitory processes, of the mobility, and later on also of the excitability. The premorbid state of the higher nervous activity has a marked effect on the course of the disease; briefly, the more intense the higher nervous activity, the sooner is the course of the disease likely to be.

[This is a most interesting paper, which unfortunately does not lend itself to abstracting.] A. Orley.


The authors, basing their conclusions on the findings in 100 selected cases of rheumatoid arthritis seen at the University Rheumatism Clinic, Zurich, including 31 in which the disease was of less than one year's duration, present a brief review of the onset and progress of this malady.

The proportion of patients showing the various classic signs of inflammation of their joints and the proportion with abnormal serum levels of iron, copper, streptococcal agglutinins, and antistreptolysin, are plotted against duration of the disease. This showed that the longer the duration, the greater the chance of the serum iron level being low [but otherwise no very impressive trends are shown].

The patients at this clinic are treated with amiodopyrine or phenylbutazone, or alternatively with salicylates if the former drugs are not tolerated. Gold is given as a standard additional therapy and the schedule employed is described. Hormonal and physical method of treatment are briefly set out.

The radiological findings in 532 instances, some of which are described and illustrated, included among others osteoporosis, erosions, and subperiosteal new bone formation. A. St. J. Dixon.

Comparative Therapeutic Trial in Rheumatoid Arthritis.


At the University Clinic, Marburg-Lahn, 47 patients with rheumatoid arthritis all in different stages were first treated with salicylates (up to 10 g. daily for 3 weeks). Those who were unable to tolerate the treatment, or did not respond favourably, or eventually relapsed within one year, were given phenylbutazone (400 mg. daily for 3 weeks). If this treatment failed an oral gold preparation "Aurubin" (2.7 mg. daily for 56 days) was then tried, and if this also failed the next treatment was ACTH (25 mg. daily for 10 days), or cortisone (50 mg. daily for 14 days), or prednisolone (10 mg. daily for 56 days). Finally, if all these treatments had failed, spa treatment with mud-baths was tried. The response to treatment was classified according to the criteria proposed by the American Rheumatology Association. As a result of these trials it was considered that spa treatment with mud-baths was the most successful. There were no controls.

[The value of this paper is greatly limited by the number of uncontrolled variables introduced and by the failure to allow for the time element; thus, although the last treatment was apparently the most successful the benefit sustained could have been equally well attributed to spontaneous improvement during the period of the trial.] G. W. Csonka.

The author describes his own method which, he claims, considers a greater variety of factors more objectively than that of Copeman and Savage. It also lends itself to presentation in the form of graphs.

He includes spontaneous and provoked articular pain, erythrocyte sedimentation rate, haemoglobin values, the need for analgesics, clinical assessment, and therapy as indices of the involvement of joints and the degree of systemic disease.

He further attempts to measure the extent of limitation of the patient’s ability to work and the degree of joint-range changes and the grip test. By compiling these factors and expressing them in numbers (0, 1, 2, 3, 4), the author arrives at a composite formula for each patient which, he hopes, will help in eliminating purely subjective data.

*L. Michaelis.*


The authors review their experiences in the treatment of 95 patients suffering with rheumatoid arthritis who had been treated in their clinic in the first quarter of 1956. Of these 95 patients, 63 had or were currently receiving steroid therapy, representing a total of 73.5 patient years of active steroid therapy. In this group, only six developed a gastro-intestinal complaint. One of these occurred in a patient being treated with hydrocortisone; five occurred in patients on prednisone, and none in patients on cortisone or prednisolone. The average dose of prednisone was 10 mg./day. Even the six affected patients did not present any serious therapeutic problems, and most of them cleared up without stopping the steroids. Indeed, the authors cast doubts as to whether the steroids were responsible for the symptoms in most of the cases.

They conclude that gastro-intestinal hazards following the use of prednisone and prednisolone are very slight indeed, and the routine addition of antacids or antispasmodics as has been suggested by other authorities seems to be unwarranted. *John Glyn.*


The author of this paper is very impressed with the value of adequate splintage in rheumatoid arthritis, and defines three situations in which splints are especially indicated:

1. When a joint is acutely painful and swollen;
2. When muscle spasm about a joint is producing deformity;
3. When subluxation has impaired function which could be improved if a limb, or part of a limb, could be held in a better position.

With regard to a development of deformity, he postulates five stages:

(i) Pain made worse by movement;
(ii) Local spasm to try to fix the joint;
(iii) Disuse leading to atrophy of the muscle fibres concerned with mobility;
(iv) Stronger flexor muscles prevailing over the weakened and elongated extensor muscles, increasing the deformity;
(v) Fibrosis and semi-permanent contractures leading eventually to bony ankylosis.

The author cites case histories with illustrations showing the uses of plasters in each of these situations. It is claimed that even the systemic illness associated with the acute stage of an arthritic process may improve greatly if the joints are properly immobilized. He stresses that the splints should be light, comfortable, and attractive. They should be worn continuously at first, and later intermittently. *John Glyn.*


This paper is the last of a series of five published by the author. (The first three have been abstracted in previous issues: *Annals of the Rheumatic Diseases*, 15, 419; 16, 157.) In the earlier papers, the author has described in detail how the various indices which he recommends are calculated and the methods by which he has attempted to validate them in terms of the clinical activity of disease. In this last paper he attempts to correlate them so as to arrive at an “index of total systemic activity”. In order to do this, he has to find a common denominator for such diverse phenomena as erythrocyte sedimentation rate, anaemia, stiffness, fatigability, muscle strength, and salicylate consumption. He achieves this by expressing each index as a percentage of the average values culled from a group of patients who had not received treatment, and he claims that this gives a consistent and reliable figure. In order to convert the observed figures for an individual patient into what are termed “percentile equivalents”, one has only to read off the figures from a comprehensive table without doing any calculations. The separate “percentile equivalents” are then added together and averaged.

The author does not claim any absolute accuracy for his figures, but does claim that the relative values for one patient at serial examinations give an accurate indication of his progress. Furthermore, he claims that the entire index can be worked out in a very few minutes, which to a casual observer seems a little doubtful in view of the apparent complexity of the measurements. It is noteworthy that in his final computations the author does not include any objective measurement of the condition of the joints themselves. This is despite an earlier paper in the series,* in which he deals with this problem in great detail, including an attempt to “weight” each joint according to the area of the joint surfaces. It is con-

cluded that while such joint measurements give an indication of the "spread" of the disease, they are not suitable or practicable as a measure of disease activity.

The author makes only modest claims for his worthy attempt to quantitate the indices of disease activity in rheumatoid arthritis. He requests only that his methods should be tried out in other centres and not accepted at their face value. Some of the principles of quantitation seem a little open to question, particularly the expression of so many diverse factors by one common numerical index. Furthermore, the attempt to evaluate the spread of the arthritic process in terms of the surface area of joints involved might be considered a little pedantic in the present state of our knowledge, and certainly too time-consuming for the average unit. However, these articles are very stimulating and will repay careful study.

John Glyn.


The authors present two clinical cases of Sjögren’s syndrome which are the first published in Portuguese medical literature. One presents the association of a very definite Felty’s syndrome.

Treated with cortisone in tablets and eyedrops and intra-articular injections of hydrocortisone, they showed very marked improvement in all the manifestations of the syndrome, maintained although slightly reduced for 5 months after the suspension of treatment apart from cortisone eyedrops and general tonics.

The cortisone eyedrops have a much more marked action on the ocular lesions than the administration of cortisone or hydrocortisone in other ways. The administration of oral cortisone and of intra-articular hydrocortisone has a marked action on the articular symptoms.

Pilocarpine is a therapeutic aid if used over short periods.

H. Moutinho.


The ocular symptoms of Still’s disease (band-shaped keratitis, chronic uveitis, and cataract) were present in two children who showed no sign of disease of the joints. The literature is reviewed and the interpretation of this clinical picture is discussed.

N. Pagliarani.


The steroid excretion in the urine was tested in four female patients with Sjögren’s syndrome. No sign of hypofunction of the adrenal cortex was found with the ACTH test. W. Leydhecker.


A child presented uveitis with a typical band-shaped corneal degeneration in one eye at the age of 3, and at 14 years of age a rheumatic affection of the knee joint.

G. von Bahr.


(Osteo-Arthritis)


The authors of this paper had recently observed a case of arthritis mutilans in which the cartilaginous lesions
had repeatedly flared up after the injudicious administration of chorionic gonadotrophins. They note some experimental work which proved that chorionic gonadotrophins can stimulate skeletal growth before puberty and are capable of producing degeneration of articular cartilage in animals. They therefore estimated the corticoids, 17-keto-steroids, and oestrogen excretion, as well as the gonadotrophin excretion in ten cases of osteo-arthritis and ten closely-matched controls.

No consistent differences between the two groups were noted, and the authors therefore conclude that the amount of gonadotrophins, as measured by available techniques, is not a factor in the aetiology of osteo-arthritis.

John Glyn.


(Spondylitis)


The records of two series of cases of ankylosing spondylitis from the Ministry of Pensions and National Insurance have been examined. One of these series, of 1,627 men, had been treated by radiotherapy; the other, of 399 men, had not been irradiated but had been treated by other methods. The expected deaths from leukaemia have been calculated and compared with those actually observed. In the non-irradiated series, 0-17 death was expected and none observed, a very good agreement between expectation and observation. In the irradiated series 0-33 death was expected and seven were observed. The odds against this excess of deaths being due to chance were greater than 1,000,000 to 1. It has thus been established that leukaemia is associated with (1) ankylosing spondylitis, or (2) irradiation, or (3) ankylosing spondylitis treated by irradiation.

The hypothesis that irradiation was the sole cause of the leukaemia was tested, but the data were insufficient to provide a firm answer. It is hoped to obtain a larger series of non-irradiated individuals by using information from the 1914-18 war, which make possible a final decision on the exact role of irradiation. The data in this survey have been discussed in the light of other independent evidence. It has been concluded that irradiation plays the main part in the production of the observed cases of leukaemia. [Author’s summary.]


The results of bone-marrow examination in 28 untreated cases of ankylosing spondylitis are reported. In three cases the peripheral blood showed mild hypochromic anaemia, the blood-counts of the remainder being within normal limits. The bone-marrow was hypercellular in 39 per cent. and of normal cellularity in the remainder. An increase in the number of lymphocytes and/or monocytes was observed in 79 per cent. In only one case was there a plasmacytosis.

The effect of irradiation of bone-marrow to a dose of 1,020-1,640 r is to cause aplasia, and this was observed in all the cases in which the marrow was examined from 2 days to 6 months after the end of treatment. Examination of the marrow from 15 months to 14 years after treatment showed that regeneration is usually incomplete. Seven of ten marrows so examined showed aplasia or hypoplasia. Examination of bone-marrow distant from the treatment areas during the 6 months following completion of radiotherapy revealed only transient changes. These were hyperplasia of erythroid precursors and hypoplasia of cells of myeloid and lymphoid series. When examination was made more than 6 months after the end of treatment, the findings were similar to those in patients who had not previously received radiotherapy. [Authors’ summary.]


The author describes the findings in 1,080 cases of ankylosing spondylitis treated at the Sanatorium for Rheumatism, Bad Bramstedt, Holstein. Predisposing factors included head lesions (38.1 per cent. of cases), trauma to the spine (8.8 per cent.), gonorrhoea and other venereal conditions (4.5 per cent.), and intestinal diseases such as dysentery or typhoid (4.5 per cent.). In 67 per cent. of the disease started between the ages of 21 and 40, but the lowest age at onset was 9 years and the highest 64. Only 6.7 per cent. of the patients were women. In 7 per cent. of cases other members of the patient’s family were affected. It was found that determination of the serum protein pattern was helpful in the diagnosis of the disease. The results of treatment were assessed by noting any increase in body height, chest expansion, and minimum finger-to-floor distance. The results of hydrotherapy combined with injections of a proprietary muscle relaxant (“Iralgin”) into the sacro-spinalis muscle are compared with those obtained from radiotherapy combined with other forms of treatment, including radiotherapy [but these methods show no significant improvement in the objective tests].

The author concludes from this study that permanent improvement can be achieved only through planned long-term collaboration between the family doctor and the specialist.

A. St. J. Dixon.
ABSTRACTS

(Miscellaneous)

Rheumatic Epicondylitis of the Humerus. (Die rheumatische Epicondylitis humeri.) Belart, W. (1956). Schweiz. med. Wschr., 86, 1279. 10 refs. The author describes 100 cases (fifty in males and fifty in females) of humeral epicondylitis seen in private practice in Zurich. Occupational strains accounted for only a few of them, but in thirty men and thirty-five women a history or physical signs of “rheumatic” pains elsewhere were obtained, mostly described as lumbar and fibrositis. Recurrences were common, in the opposite arm as well as in the same arm. Various clinical forms of the condition could be distinguished. Treatment consisted in the injection of tuberculin, or injecting the lesion with hydrocortisone; the latter proved the more effective.

A. St. J. Dixon.

New Aspects of the Aetiology of Sjögren’s Syndrome. McLenachan, J. (1956). Trans. ophthal. Soc. U.K., 76, 413. 6 tab., 5 figs, 29 refs. A survey of 45 cases of Sjögren’s syndrome. There was evidence that liver dysfunction was present in the majority of cases. The author makes a comparison between Sjögren’s syndrome and vitamin A deficiency and suggests that an inability to utilize vitamin A may explain the epithelial changes throughout the body.

C. A. G. Cook.


Mechanism of the Therapeutic Action of Ultrasound. (Sui meccanismi di azione terapeutica ultrasonora.) Radino, G. (1957). Reumaitismo, 9, 71. 6 refs.


Antithyroid Effect of Phenylbutazone. [In English.] Castenfors, H., Lovgren, O., and Allgoth, A. M. (1956). Acta rheum. scand., 2, 244. 3 figs, 6 refs.


Assessment of Mobility in Joints. Williams, P. O. (1957). Rheumatism, 13, 13. 3 figs, 2 refs.


Disk Syndrome


Treatment of Sciatica with Hydrocortisone by the Sacral Epidural Route. (Il trattamento idrocortisonico per via epidurale sacrale delle lombosciatalgie.) Cappio, M. (1957). Reumatismo, 9, 60. 12 refs.


Gout


The authors, from the University of Colorado, Denver, describe the results of oral phenylbutazone therapy in sixty acute attacks of gout in 42 men. The response was assessed subjectively by the degree of relief of pain and also objectively by observing the time taken for manifestations of the arthritis to subside. There was complete control of pain within 24 hours in 56 of the sixty attacks, some relief being obtained in 2 to 4 hours. The relief and control of pain were correlated with the attainment of a serum phenylbutazone level of approximately 3 mg. per 100 ml., and this could be achieved by administration of a large initial dose of from 400 to 800 mg. phenylbutazone. In 47 of 51 attacks, all objective evidence of arthritis had resolved within 72 hours, and to attain this result the administration of from 100 to 200 mg. four times daily for 3 to 4 days was found to be best. One patient passed a melaena stool 8 days after treatment, and "occasionally a patient complained of mild epigastric burning". Otherwise there were no undesirable side-effects, and it is concluded that phenylbutazone is less toxic than colchicine and that acute gouty arthritis responds dramatically to its use.

J. Warwick Buckler.


Pararheumatic (Collagen) Diseases


In this paper from the University of Oregon Medical School the author gives the clinical histories of two patients suffering from systemic lupus erythematosus in whose blood circulating anticoagulants were present.

During a relapse the first patient developed thrombocytopenic purpura. Investigation showed a prothrombin concentration of 57 per cent., and bleeding and coagulation times were both more than 30 minutes. When mixed with normal blood the anticoagulant from the patient's blood was found to inhibit coagulation at a dilution of 1:10. The anticoagulant is thought to be an anti-thromboplastin factor. After 6 months' prednisone therapy the patient is in good health and there is complete absence of circulating anticoagulant.

The second patient had both acute systemic lupus erythematosus and active pulmonary tuberculosis. Although there were no haemorrhagic manifestations, laboratory tests revealed a circulating anticoagulant with properties similar to that in the first case.

E. G. Rees.


The author of this paper from Jersey City Medical Center, New Jersey, states it as his purpose "to report this condition [collagen disease of the small bowel] in its early and late stages so that it can be readily recognized clinically in the operating room and possibly treated earlier". Full details of three cases are presented.

Case 1 was in a man of 47 years, Case 2 in a Negress aged 35, and Case 3 in a man aged 23.

All three patients presented with upper abdominal pain of a duration of 6 months to one year. This was related to food in Cases 1 and 3, and was accompanied by abdominal distension in Cases 2 and 3, by vomiting in Cases 1 and 2, and by nausea only in Case 3. Bowel action was normal in Cases 1 and 3, while diarrhoea and melaena occurred in Case 2. Loss of weight was complained of in all cases, the loss varying from 10 to 23 lb. (4.5 to 10.4 kg.). Physical examination revealed little except evidence of weight loss in Cases 1 and 2, while there was diffuse epigastric tenderness with slight guarding in Case 3. All three patients underwent exploratory laparotomy. Surgical treatment in Case 1 consisted in intestinal resection and anastomosis; the patient survived, but the long-term benefit is considered to require time and also many more recorded cases to elucidate. In Case 2 the patient's condition deteriorated, and she died 2½ years later after resection of a small piece of bowel for biopsy. In Case 3 the disease was found to be so widespread as to render definitive intervention impossible, and a biopsy only was taken.

The diagnosis of collagen disease of the small bowel is discussed on the basis of the above cases. The condition may be accompanied by scleroderma or Raynaud's phenomenon. Diagnosis is suggested by the characteristic x-ray findings of dilated bowel, with barium retention and diminished peristalsis, but these signs are not
always present. The gross appearances of the early stages include oedema, diminished tone and peristalsis, increased calibre of the bowel, dilated radial lymphatics filled with a white substance, and enlarged soft lymph nodes. Later the small bowel shows a white, sclerosed serosal surface, diminished tone and peristalsis, and hard lymph nodes. Free peritoneal fluid was not seen in any of the cases.

Confirmation of the diagnosis rests on the microscopical demonstration of replacement of the muscularis, and subserosal and submucosal infiltration by collagen. Post-mortem examination may reveal sclerosis of the heart, kidneys, spleen, or bone. L. G. Fallows.

Corticotrophin and Cortisone Therapy in Dermatomyositis.

The author, in this communication, reports the results of treatment with corticotrophin or cortisone of three cases (all in females) of dermatomyositis at Newcastle General Hospital. The first patient, aged 30, presented with a widespread myositis and facial erythema. The disease progressed rapidly despite administration of antibiotics and salicylates. Response to corticotrophin treatment was prompt and dramatic, the patient surviving an abortion accompanied by considerable uterine haemorrhage during its course. Treatment was discontinued after a total of 5 g. corticotrophin had been given, at which time recovery was complete. The second patient, aged 49, was admitted with extensive myositis, and later developed lower motor neurone lesions of both hands. The disease was further complicated by a severe purulent bronchitis. Urinary creatine excretion was within normal limits. Again antibiotics proved unsuccessful, but there was a rapid and apparently complete recovery following treatment with corticotrophin to a total dosage of 2.2 g. The third patient, aged 47, was admitted in a critical state and was immobilized by extensive muscle involvement. Urinary creatine excretion was raised, and muscle biopsy showed oedema and round-cell infiltrates. A good response to corticotrophin was obtained in the initial stages of the disease, but later both soft-palate palsy and inhalation pneumonia developed and the patient died.

After a comprehensive review of the literature the author concludes that corticotrophin may be life-saving in acute fulminating dermatomyositis; it is, however, less useful in the more chronic form of the disease, though, in view of the occasional success claimed in this category, it should never be withheld.

J. N. Harris-Jones.

The authors report from the Mayo Clinic the results of a histopathological study of the cutaneous lesions in 38 cases of systemic and three cases of chronic discoid lupus erythematosus (L.E.).

The diagnostic changes, which are described, included follicular plugging, hyperkeratosis but no parakeratosis, liquefactive degeneration of the basal layer, and lymphocytic infiltration. Fibrinoid changes in the vessels were not frequent (five out of 38 cases), and aggregates of karyorrhexic nuclei even less so (two out of 38 cases). Differentiation between systemic and chronic discoid forms of L.E. has been found almost impossible, the histological changes being related more to the age of the lesions than to the clinical type of the disease. The diagnostic features became clear when the lesions were about 4 weeks old, but up to this time the histological changes were non-specific.

The basement membranes of the epidermis, hair follicles, and sweat glands stained strongly positive with periodic-acid-Schiff and were swollen or fragmented. The histiocytes in these situations revealed intense macrophagic activity. An increase in the numbers of mast cells was also observed. Performance of a modified Brachet test (methyleneblue stain controlled by ribonuclease and perchloric acid extraction) demonstrated the presence of "red bodies" derived from the nuclei of lymphocytes, and to a lesser extent from those of connective-tissue cells, through depolymerization of deoxyribonucleic acid; these "red bodies" appear to be non-specific for L.E. On the other hand metachromasia, as revealed by staining with toluidine blue, occurring both intracellularly and extracellularly, is considered to be characteristic of the disease. Staining was controlled by the use of hyaluronidase, acetylation, sulphation and oxidation by chronic acid; the results were found to be suggestive of a pathological modification in the synthesis of mucopolysaccharides by the connective-tissue cells. Sudan black B showed round cytoplasmic inclusions in macrophages in five out of the 38 cases.

A. Swan.


Of 156 patients with chronic discoid lupus erythematosus treated at Dundee Royal Infirmary (University of St. Andrews) since May, 1952, with either mepacrine or chloroquine, those classed as "much improved" and "improved" all relapsed within one year to their pre-treatment status, while out of 41 who were classed as "clear", only eight remained free of lesions after 2 years. It was found, however, that when therapy was resumed the condition usually cleared up again, and also that the interchanging of chloroquine for mepacrine or vice versa was effective in some cases. Continued treatment with a small maintenance dose for several months after apparent cure is therefore advised.

Of 24 cases of light-sensitive summer eruption which were treated with chloroquine, the eruption disappeared during the summer in thirteen, was improved in seven, and was not influenced in four. In the thirteen controlled cases the eruption recurred in the following spring.

Such a very high relapse rate does not correspond with the abstracter's own experience.

E. W. Prosser Thomas.
Muscular Lesions in 46 Cases of Collagen Disease.

At the Institute of Pathology, Geneva, examination of the skeletal musculature of 46 patients suffering from one of the "collagen diseases" showed histological evidence of muscle damage in 32 cases, that is, in seventeen out of 25 patients examined by muscle biopsy and in fifteen of the 21 cases coming to necropsy. Clinical evidence of muscle damage was observed in only ten patients. The cases with histological signs of muscle involvement included five patients with rheumatoid arthritis, four with disseminated lupus erythematosus, three with scleroderma, eleven with periarteritis nodosa, and nine with sarcoidosis. No lesions in the skeletal muscles were found in 88 other subjects, suffering from various conditions, such as tuberculosis, cirrhosis of the liver, and neurological and cardiovascular disorders.

The histological picture in the various collagen disorders was similar and consisted in alterations in the ground substance, angiitis, and the formation of foci of inflammatory cells, mainly lymphocytes and histiocytes. The author considers that the muscle damage observed in many of these cases is secondary to the changes in the interstitial tissue and probably is mainly due to the angiitis. [Similar conclusions were reached in an investigation of the damage to cardiac muscle occurring in rheumatic carditis carried out by the abstractor (J. Path. Bact., 1954, 68, 101; Abstracts of World Medicine, 1955, 17, 8).] The degree of muscle damage found varied considerably and was severe in three cases. Thus, apart from the characteristic lesions of periarteritis nodosa and sarcoidosis no specific histological picture could be defined for any of the other collagen diseases.

B. Ruebner.

Ocular Changes in Periarteritis Nodosa. BOECK, J. (1956 (Part I)). Amer. J. Ophthol., 42, 567. 5 figs, bibl.

Writing from the Second Eye Clinic, University of Vienna, the author discusses the ocular changes in periarteritis nodosa. These changes, which may be very varied, are considered under three headings:
(a) those of local periarteritis nodosa in the eye;
(b) those which are part of or sequelae of generalized periarteritis nodosa;
(c) active tissue changes occurring independently of periarteritis though possibly due to a cause common to both conditions.

With regard to the first group, attention is drawn to the frequency of peripheral choroidal lesions in cases in which the retinal vessels may show no definite changes, or when the retina shows gross albuminuric retinopathy. But this latter condition, which is found in many advanced cases of the disease, is not considered to be a manifestation of periarteritis nodosa. Changes in the choroidal vessels consist chiefly in fibrinoid degeneration amounting to total occlusion, while in others cellular proliferation may be found in the vessel lumen. The possibility arises whether retinal serous detachment is secondary to these changes in the choroid. Although the aetiology of periarteritis nodosa remains unknown some consideration is given to theories of a specific virus infection, similar to that of herpes zoster. P. Jameson Evans.


A man aged 33 with unilateral exophthalmos was repeatedly observed and his general condition thoroughly investigated over a period of nearly 5 years until his death. The original diagnosis of pseudo-tumour was maintained and confirmed after 2 and again after nearly 3 years by biopsies of orbital tissue.

Although treated with thiouracil and thyroid for 4 years and then with cortisone for 5 months, the cause of the pseudo-tumour remained in doubt. Haemorrhagic and rheumatic features increased greatly shortly before his death. Post-mortem findings disclosed arteriolar polyarteritis.

Periarteritis nodosa is discussed with regard to its clinical features, aetiology, and pathology, and the various ocular complications are reviewed.

Howard Coverdale.


Rheumatoid Arteritis and Periarteritis Nodosa. (Reuma

Pulmonary Form of Disseminated Lupus Erythematosus. (Die pulmonale Form des Lupus erythematosus dissem


Non-Articular Rheumatism


"Myelofibrosis" and "myelosclerosis" are terms used to describe a rare condition in which the bone marrow is replaced by fibrous tissue or by bone, thirteen cases of which are reported from the Royal Infirmary, Edinburgh. The syndrome, the cause of which is unknown, probably belongs to a group of proliferative disorders affecting the primitive mesenchymal cells and is thought to be closely related to myeloid leukaemia, polycythaemia vera, and megakaryocytic leukaemia. It occurs most frequently in the fifth and sixth decades, the symptoms being weakness, lassitude, dyspepsia, and abdominal discomfort and pain, especially in the left quadrant. Splenomegaly, sometimes very pronounced, is a common feature; hepatic enlargement is less marked. The peripheral blood picture is generally that of a leucoerythroblastosis, but other haematological findings are variable. In some of the cases the haemoglobin level and the total leucocyte and platelet counts were normal, while in others profound anaemia, polycythaemia, leucocytosis or leucopenia, or thrombocytosis or thrombocytopenia occurred. The proportion of primitive cells (myelocytes and metamyelocytes) varied from 10 to 20 per cent. of the leucocyte count. Failure or difficulty in obtaining a specimen of bone marrow by sternal or iliac-crest puncture is regarded as diagnostic. When marrow was obtained by sternal trephine, myelofibrosis and large numbers of megakaryocytes were demonstrated. Evidence of extramedullary haematopoiesis was found in some instances by biopsy of the lymph nodes, liver, and spleen.

Radiological changes in the bones were observed in eight of the thirteen cases. In five cases where these were absent, and in three where they were confined to alteration in the trabeculation of the cancellous bone of the humeri and femora giving an appearance of "meshwork", proliferation of fibrous tissue (myelofibrosis) was the predominating feature. In the remaining five cases, the bone changes were more marked and widespread, with replacement of cancellous bone by thickened trabeculae, and in these the marrow condition was suggestive of myelosclerosis. These more severe radiological changes were considered to be a valuable aid to diagnosis but they could not be correlated with the severity or duration of the disease.

Discussing treatment, the authors conclude that splenectomy is not warranted in the majority of cases, but may be justified when symptomatic haemolytic anaemia or a tendency to haemorrhage necessitating frequent blood transfusions develops, or the spleen becomes so large as to cause severe pain or discomfort. In four of the thirteen cases subjected to splenectomy, the operation had no influence on the clinical condition in three, but was of great benefit in one; in all four cases, however, it has been followed by progressive enlargement of the liver, and in three by an increase in the number of leucocytes and normoblasts. Radiotherapy of the spleen in one case produced a very satisfactory result. It is suggested that carefully controlled irradiation of the spleen should be considered in cases with gross splenomegaly, but that such a procedure should not preclude splenectomy if required at a later date.

_Ethel Browning._


In this paper the author develops a theme which he originally propounded in 1953. He believes that rheumatoid disease can occur in the complete absence of joint involvement and that although the pathology appears to be identical with rheumatoid arthritis, the prognosis is generally much better.

He records seventeen further cases of anarthritic rheumatoid disease, and four other cases in which the involvement of the joints was minimal. These form a link between the two forms of rheumatoid disease.

The syndrome occurs mainly in the middle-aged and elderly. It frequently presents as pyrexia of unknown origin with associated anorexia, loss of weight, anaemia, and general malaise. There is often associated abdominal discomfort and headaches. With regard to the musculoskeletal system, there is generalized aching and stiffness in the muscles, characteristically most severe in the neck, shoulders, and back. Active movements of the joints may be restricted by pain, but there is no obvious arthritis present. Rheumatic nodules and rashes may appear in the skin. There is generally a very high sedimentation rate, usually around 100 mm. in one hour (Westergren) and often well above this (the range in the series was 25 to 148 mm.). The average haemoglobin figure was 11-2 g. per 100 ml. The white cell count is usually normal. The bone marrow often showed slight plasmocytosis, and there was a relative decrease in the plasma albumen and an increase in the alpha-1, alpha-2, and gamma globulin fractions. Cryoglobulins were occasionally present, and the differential sheep-cell agglutination tests were definitely positive in three cases and probably positive in four others. The x ray of the joints did not reveal any pathology except occasional osteo-arthritis. The duration of the symptoms averaged 5 1/2 years (with a range of 3 months to 35 years) and in at least eight of the patients there was a history of emotional stress preceding the onset of symptoms. The response to salicylates was moderate only. The author states that the prognosis is invariably good despite the occasional persistence of symptoms for many months.


General Pathology


In the opinion of Wood and others C-reactive protein is most likely a β globulin. It has also been shown that the basic component of the precipitate which forms when carbon dioxide is bubbled through diluted human serum is mainly β globulin. On the basis of these two facts the authors, working at the Research Institute of Rheumatic Diseases, Prague, passed carbon dioxide through diluted serum obtained from a patient in the acute stage of rheumatic fever. From the resulting precipitate an antiserum was prepared that was specific against precipitate-antigen. This was then absorbed on to collodion particles, and after incubation for 60 minutes at room temperature followed by centrifugation these were found to be agglutinated by the serum of patients with acute rheumatic fever, rheumatoid arthritis, myocardial infarction, and diffuse glomerulonephritis. The details of the preparation of the antiserum are described, together with procedures used to check its specificity against the antigen in the carbon dioxide precipitate. The results seem to confirm that this precipitate is chiefly β globulin with probably a small admixture of α and γ globulins, and from the clinical results it seems probable that it includes C-reactive protein.

In a clinical study the serum of more than forty patients with rheumatic fever was tested with the antiserum. The charts (reproduced) of four cases show that the result of this test followed closely the results for erythrocyte sedimentation rate (E.S.R.) by Westergren’s method.

The reaction was also found to precede a rise or fall in the E.S.R. by several days, or even to give a positive result when the E.S.R. was normal. In the fourth case treatment with cortisone appeared to deprive the test of its sensitivity. The test thus gives results very similar to the test for detection of C-reactive protein. The antiserum is claimed to be simpler to prepare than that for the detection of C-reactive protein, but since it loses its potency within 48 hours it must be freshly prepared, thereby making the test more complicated than the detection of C-reactive protein for which commercial antisera are available.

G. H. Blair.


This report details and analyses the authors’ experiences with sheep-erythrocyte agglutination tests for rheumatoid arthritis carried out at the Rheumatism Research Centre, Aix-les-Bains, and the Institut Pasteur, Paris, in which they used a technique of sensitized sheep-cell agglutination after adsorption of heterophil agglutinins, similar to that of Svartz and others and of Heller and others; a titre of 1 in 48 was taken as the dividing line between a negative and a positive result.

Out of a total of 707 tests on 642 patients or controls they found positive results as follows: rheumatoid arthritis (R.A.), including juvenile R.A., 265 out of 477; ankylosing spondylitis, six out of 124; gout, one out of seventeen; arthritis associated with psoriasis, one out of thirteen; rheumatic fever, nil out of eleven; and in healthy control subjects, two out of 65. The test was more often positive in R.A. when nodules were present, but in eleven of the cases of R.A. with nodules the reaction was negative. There was a rough correlation between the agglutination titre in R.A. and the erythrocyte sedimentation rate, and also with the duration of disease, but none with loss of weight or with variations in the pattern of the serum proteins as revealed by paper electrophoresis. In 379 cases comparison of this technique with the Waaler-Rose technique, and in 351 sera with the “serum erythrocyte agglutination” technique of Heller and others, showed it to be more reliable than either of these two methods. The test also helps to differentiate between the various symptoms of chronic polyarthritis.

A. St. J. Dixon.


The synovial fluid of patients with rheumatoid and other, unrelated, arthritic conditions is known to have a viscosity lower than that in normal joints. It has been shown that the viscosity of synovial fluid is related to the concentration of hyaluronic acid and particularly to the degree of polymerization of its molecules. This paper from Wayne University College of Medicine, Detroit, presents results on the basis of which it is contended that the “intrinsic viscosity” provides a more reliable assessment of the mean degree of polymerization. Intrinsic viscosity is defined as “the increase in viscosity divided by the concentration, extrapolated to zero concentration”. This determines the volume required by a molecule during flow in the limit of extreme dilution, and hence for a given type of polymer is related directly to the degree of polymerization.

Synovial fluid was obtained from 25 rheumatoid arthritic knee-joints and post mortem from nine normal joints and some 25 joints showing other arthritic conditions. When an insufficient volume of fluid was available further fluid was obtained by washing out the joint with physiological saline, this procedure being shown to provide equally satisfactory and identical readings. Protein was removed by agitation the fluid for one hour with chloroform, and the hyaluronic acid content was estimated by the carbazole method of Dische. Intrinsic values of fluid from normal knee-joints gave a mean value of 69.3 ± 4.2 units, whereas the fluid from 25
**ABSTRACTS**

Rheumatoid arthritic knee-joints showed a mean value of 37.6 units, only two results being over 55 units. Fluids from cases of traumatic arthritis (32-5 units), acute pyogenic arthritis (54-70 units), osteoarthritis (49-8 units), tuberculous arthritis (one case) (4 units), acute systemic lupus erythematosus (54-2 units, range 21 to 83), gouty arthritis (50-7 units), and several cases of rheumatic fever and scleroderma all gave mean values below the normal. Synovial fluid from a case of myxoelemma showed the highest concentration of hyaluronic acid and the highest relative viscosity, but the intrinsic viscosity was well below the normal, at 42 units. Systemic and intra-articular steroid therapy resulted in only slight increase in the viscosity, which was more closely related to increase in hyaluronic acid, although the clinical results were good.

In view of these findings it is suggested that de-polymerization of hyaluronic acid is not specifically associated with rheumatoid arthritis. The measurements had no relation to the clinical or laboratory evidence of the severity or activity of the rheumatoid disease process, and the results achieved with steroid therapy indicate that the polymerization of hyaluronic acid is unrelated to the inflammatory processes.

*Harry Coke.*


Systemic amyloidosis was diagnosed in two cousins, aged 50 and 52 years, referred to the Hospital of the University of Michigan, Ann Arbor, because of an unusual syndrome. The chief symptoms were increasingly defective vision and numbness and pain in the hands and legs. Ophthalmic examination revealed the presence of semi-opalescent, hyaline-like opacities, while neurological investigation suggested a peripheral neuropathy. The diagnosis was confirmed by skin biopsy in one case and at necropsy in the other. Electrophoresis of the serum proteins in both cases revealed the presence of an unusual fraction “migrating between the β and α₂ globulin areas”.

A study of some 66 relatives of these patients showed that in 37 the electrophoretic pattern of the serum was normal, in fifteen there was an abnormal peak between the α₂ and β globulins, and in fourteen the pattern was characterized by poor resolution in the α₂ region. The serum lipoprotein concentration was determined in 33 of these relatives by ultracentrifugation. Abnormalities in lipoprotein distribution were uncommon, and were highly correlated with the abnormalities detected by serum electrophoresis.

In many of the members of this family there were clinical signs and symptoms suggestive of amyloidosis, these being most marked when the serum protein pattern was abnormal. Thus, in ten of the fifteen subjects showing an atypical peak between the α₂ and β globulins, and in six of the fourteen whose electrophoretic pattern was poorly resolved in the α₂ region, there were clinical signs and symptoms suggestive of the disease. Of the thirteen subjects with an abnormal electrophoretic pattern but no clinical manifestations of the disease, twelve were under the age of 21.

These abnormalities were distributed in the family in a manner consistent with the hypothesis that a single disease process was being inherited as a Mendelian dominant character. The earliest sign of the disease is evidently to be found in the abnormal character of certain of the serum globulins. Clinical signs and symptoms may not develop till later in life, and are rather variable.

*H. Harris.*


**ACTH, Cortisone, and Other Steroids**

**Controlled Trial of Effects of Cortisone Acetate in Chronic Asthma.** Medical Research Council Sub-committee on Clinical Trials in Asthma (1956). *Lancet*, 2, 798. 5 refs.

The report of the subcommittee appointed by the Medical Research Council to investigate the value of cortisone acetate in chronic asthma is presented. The trial was carried out at five centres in London and one in Manchester. Patients with severe broncho-pulmonary infection, cardiac failure, or tuberculosis were excluded from the trial, and only those patients were included who were between 14 and 60 years of age, had a history of asthma of not less than 3 months’ duration, and had not had complete remission for more than 2 weeks during the preceding 3 months. In all, 96 patients were studied, 49 receiving cortisone and 47 (the control group) a placebo. The groups were constituted by random allocation, and although there was a slightly higher proportion of younger women in the control group, they were otherwise comparable. The dosage of cortisone was 300 mg. on the first day, 200 mg. on the second, and 100 mg. on each of the next 4 days, the subsequent dosage being adjusted to the patient’s requirements. Nearly all the patients in both groups also received some antispasmodic therapy when this was considered to be necessary.
The trial lasted 24 weeks, during which time ten controls and nine test patients had to be withdrawn for reasons given. Whereas at the beginning of the trial the cortisone-treated patients seemed to benefit, by the end of the trial there was no significant difference between the groups, either in regard to greater capacity for work or to the amount of antispasmodics required. The vital capacity fluctuated in both groups of patients. Two patients developed status asthmaticus in spite of receiving 100 and 75 mg. cortisone respectively daily.

Kate Maunsell.


The effectiveness of cortisone in status asthmaticus was compared with that of antispasmodic drugs in a clinical trial carried out at thirteen different centres in Great Britain by a subcommittee appointed by the Medical Research Council [see previous Abstract]. No patient who was under 14 years of age or who had not had at least one severe attack of asthma was included in the trial. During the first 24 hours after admission the patient's usual treatment with well-established drugs was given and only those patients were finally selected for the trial who did not respond satisfactorily. These patients were divided into two groups at random, the first receiving cortisone acetate and the second a placebo, the patient's standard treatment being continued in both groups as required. Cortisone, in divided doses, was given as follows: 350 mg. on the first day, 200 mg. on the second, after which the dose was progressively reduced by 25 mg. daily until the ninth day, the total amount of cortisone administered then being 1·25 g. The treatment of patients with placebo tablets only, without standard treatment, was rejected on ethical grounds and for similar reasons it was agreed that treatment could be discontinued or changed as thought necessary in any particular case during the trial.

As a result of exclusion for various reasons only 32 patients finally participated in the trial, fifteen receiving cortisone and seventeen the placebo. Among the former, ten were relieved of disabling bronchial obstruction by the fourth day, whereas only four of the seventeen control patients were so relieved, but by the end of 3 months' follow-up all of these improved patients had reverted to their former asthmatic condition. Kate Maunsell.


In the first of these two papers the author describes studies carried out at Brooklyn Hospital, New York, in which it was shown that the addition of iso nicotinic acid hydrazide (isoniazid) in concentrations of 0·5 to 15·0 "milligrams per vessel" reduced the destruction of cortisone acetate by rat liver slices in vitro. [Few details are given.]

The clinical application of this finding is described in the second paper. In this study isoniazid in doses of 100 to 600 mg. per day, together with cortisone acetate, 37·5 mg. per day, was given by mouth to 39 patients with rheumatoid arthritis, nine of them being treated for over 2 years, and 24 for over one year. All improved, and a complete remission was obtained in three cases. In the remaining 36 cases withdrawal of either drug produced a relapse of disease.

The authors conclude that isoniazid potentiates the action of cortisone by inhibiting the destruction of the latter in the liver.

[This report is unconvincing without further detail.] Allan St. J. Dixon.


A study of the potency of various adrenocortical hormones and some of their analogues, with special reference to rheumatic diseases, is reported from the Mayo Clinic. One patient who had severe rheumatoid arthritis was given 20 mg. prednisone daily for 36 days, and, after a rest period of 12 days, 80 mg. hydrocortisone (free alcohol) daily for 24 days; this was followed by prednisone in a dosage of 20 mg. daily for 6 days, 15·5 mg. for 6 days, and 15 mg. for 6 days. Prednisone and hydrocortisone in these dosages had equally satisfactory antirheumatic effects and the erythrocyte sedimentation rate tended to return to normal. Prednisone had little effect on the plasma potassium concentration, which, however, decreased during administration of hydrocortisone. The haematocrit value increased and body weight decreased during treatment with prednisone, but no such changes were observed in response to hydrocortisone.

Discussing the problem of hypercortisonism, the author stresses that temporary relief may be obtained from an alteration in dosage of the drug. The muscular and articular aching which accompanies this syndrome is unlike that associated with an exacerbation of the rheumatoid arthritis. Synovitis is minimal and symptoms are relieved by rest. The syndrome may give rise to a variety of mesenchymal reactions, which in some instances are irreversible and death results. Of 128 rheumatoid patients with chronic hypercortisonism, eighteen had L.E. cells in the plasma or bone-marrow or both, and temperature exceeded 100·0 F. (37·8° C.). In five patients panarteritis histologically identical with periarteritis nodosa developed.

Discussing the dosage of these hormones in chronic rheumatic conditions the author states that the optimum dosage in women after the menopause is 20 to 30 mg. cortisone or 3·5 to 5 mg. prednisone daily, while before the menopause the daily dosages are 30 to 37·5 mg. and...
5 to 6.5 mg. respectively. In adult males the optimum dosage is 37.5 to 50 mg., cortisone or 6 to 9 mg., prednisone daily. The hormones are tolerated by 50 to 60 per cent. of the patients in whom they are indicated, and active signs of disease are controlled in about 75 per cent. of them.

D. Freiskel.


In women with rheumatoid arthritis the excretion of androsterone and etiocholanolone was employed as an indicator of the adrenal steroid secretion. The action of cortisone, cortisol, \( \Delta^1 \)-cortisol and ACTH on this secretion was investigated.

Daily administration of 40 mg. cortisol or 50 mg. cortisone resulted in depressed adrenal cortical secretion. Even when such medication had been given for 3 to 12 months, however, relatively small doses of ACTH in most cases stimulated endogenous steroid production. A schedule has been drawn up, according to which ACTH is given intermittently during steroid administration. By this means the above-mentioned hazards of prolonged steroid therapy may be avoided. The ACTH in the schedule can stimulate the adrenals to marked steroid production although corticosteroids are concurrently given. Inhibition of the adrenal steroid secretion was recorded when \( \Delta^1 \)-cortisol was given in a dosage of 30 mg. per day. [Authors' summary.]


A test for adrenal cortical insufficiency, by observing the capacity of the adrenal cortex to respond to ACTH stimulation, was investigated at Marquette University School of Medicine, Milwaukee. In each case urine was collected for two 24-hour periods to determine control values for 17-ketosteroids and corticosteroids. During the three subsequent days corticotropin was administered. Urine collections were continued during this period and on the two following days, and steroid values compared with the control values. The excretion of 17-ketosteroids was determined by the Callow-Zimmerman method (Endocrinology, 1943, 33, 229); that of corticosteroids by the sodium bismuthate method of Norymberski (Biochem. J., 1953, 55, 371). Corticotropin was administered by two methods:

1. 35 patients were given 20 or 25 U.S.P. units corticotrophin in a 5 per cent. dextrose solution intravenously over a period of 5 to 6 hours daily for 3 days;
2. 22 patients were given 40 commercial units of an intramuscular repository corticotrophin preparation every 12 hours for 3 days.

All these patients suffered from a variety of acute and chronic diseases. For comparison similar tests were carried out on four patients with Addison's disease and six patients with anterior pituitary insufficiency.

The maximum increase in steroid excretion usually occurred on the third day of corticotrophin administration; exceptionally it occurred either before or after. With control values of steroid excretion greater than 2 mg. in 24 hours, increments greater than 100 per cent. in either 17-ketosteroid or corticosteroid excretion were considered an adequate response; when control levels were less than 2 mg., only increments over 200 per cent. were considered significant. By these criteria only three of the 57 patients failed to respond adequately. If 17-ketosteroid determinations alone are considered, the number of failures is quite high; with corticosteroid excretion alone it is less; when both are considered, only the small percentage of patients with intact adrenals failed to respond. Intramuscular injection of corticotrophin produced more pronounced and prolonged stimulation of the adrenals than did intravenous administration.

The response in six patients with anterior pituitary insufficiency was similar to that of the control group. In the four patients with Addison's disease the urinary steroid values did not significantly change when corticotrophin was administered. Kenneth Stone.


It is pointed out that urinary excretion of aldosterone can be regulated by changes in the volume of body fluid. Further, some workers have found that corticotrophin (ACTH) stimulates aldosterone secretion, but the evidence for this is conflicting, and the present authors, in this paper from the University of Geneva, describe an investigation of the part played by ACTH in regulating aldosterone secretion in healthy subjects receiving a constant diet and fluid intake. In all subjects the blood level of corticoids and the urinary excretion of 17-hydroxycorticoids and of aldosterone were determined.

In a preliminary trial on eight subjects without dietary control ACTH appeared to stimulate urinary excretion of aldosterone, but the effect was variable. Further experiments showed that whereas no significant rise in aldosterone excretion occurred after ACTH in a subject whose intake of sodium was normal, in two subjects whose sodium intake was restricted to 10 mEq. daily aldosterone excretion increased markedly after ACTH. A diurnal rhythm in excretion of the hormone was also demonstrated, larger quantities being excreted in the daytime. The authors state that although the effect of ACTH on aldosterone excretion appeared to be rapid it was of short duration.

It was also found that if ACTH was given to a subject on a low-sodium diet when the effect of vasopressin and water was wearing off and body weight was decreasing, urinary excretion of aldosterone increased to six or seven times the control amount. In one subject, however,
whose weight continued to increase on this regimen the effect was less marked.

In the authors’ view the results indicate that ACTH can stimulate adrenal production of aldosterone. However, since fluid retention occurs at the same time and this directly inhibits aldosterone secretion, the resultant effect will vary, depending on the relative preponderance of the two factors—that is, whether the subject gains weight or loses weight while the ACTH is being administered.

Denis Abelson.


In the original Thorn test the fall in the eosinophil count 4 hours after one intramuscular injection of 25 mg. ACTH was taken as an expression of adrenocortical response, a fall of over 50 per cent. being regarded as a sign that adrenocortical function was satisfactory. It soon appeared, however, that local changes at the site of injection tended to cause a “resistance”, especially in patients who had previously received ACTH, thus producing a lack of eosinophil response and giving rise to misleading test results in some 7 or 8 per cent. of cases. Thorn then introduced the 48-hour test, in which intramuscular injections were given every 6 hours and the fall in the eosinophil count and the increase in urinary 17-ketosteroid excretion were observed. Later, he introduced the 8-hour intravenous infusion test with ACTH as a quantitative measure of adrenocortical stimulation, but Thorn himself gave the warning that any such infusion in a patient with untreated Addison’s disease might have grave consequences.

The authors, working at the Medical Clinic, Toulouse, have therefore used a delayed-action preparation of ACTH in zinc phosphate, of which they gave a single intramuscular injection of 40 units (2 ml.) at 8 a.m., eosinophil counts being carried out before the injection and 8, 14, 18, and 22 hours thereafter. The urinary 17-ketosteroid and 17-hydroxysteroid excretion was also estimated the day before and on the day of the test. Of the 52 subjects examined, 32 were healthy, nine were patients with Addison’s disease (two untreated), five had haemochromatosis, and six were obese. In the normal subjects, the fall in the eosinophil count exceeded 90 per cent., and the urinary excretion of 17-ketosteroids and 17-hydroxycorticosteroids was significantly increased on the day of the test, the results being comparable to those of the 8-hour infusion test. In the patients with Addison’s disease the eosinophil count never fell below 50 per cent. and the urinary steroid excretion was not increased, but there were no untoward symptoms. In the five patients with haemochromatosis, the results were variable; the urinary steroid excretion was unchanged. In the obese patients ACTH given intramuscularly had no influence on the eosinophil count or the steroid excretion, probably because of local inactivation by the fatty tissue. The test would, therefore, appear to be invalid in obese patients. V. C. Medvei.


The authors present their observations on adrenocortical deficiency as seen in 44 patients, of whom seventeen had undergone total, and 27 subtotal, adrenalectomy for hypertensive disease at the University of Pennsylvania Hospital, Philadelphia, and compare them with those in nine cases of spontaneous Addison’s disease. In the performance of subtotal adrenalectomy about 5 per cent. of one adrenal gland was left. Replacement therapy consisted in the oral administration of cortisone, in some cases supplemented with deoxycortone, and a normal salt intake. Residual adrenocortical function was assessed in several ways. The minimum hormone requirement, as determined by the level at which clinical signs of insufficiency developed, was greater after total than after subtotal adrenalectomy, and if no maintenance therapy was found to be necessary either regrowth of residual adrenal tissue or the presence of accessory tissue could be assumed. The addition of deoxycortone seemed to have little effect in some cases, but in others enabled the maintenance dose of cortisone to be considerably reduced. The stimulating effect of corticotrophin (ACTH) was also studied. The authors found that a reduction in the circulating eosinophil count of even 65 per cent. was not a good index of adrenal response, and the urinary level of 17-ketosteroid excretion could also be misleading. However, the latter estimation and that of total urinary neutral reducing lipids after hydrolysis of the urine with β-glucuronidase were more reliable than the determination of urinary reducing lipids after acid hydrolysis.

Skin pigmentation was less frequent in adrenalectomized patients than in those with spontaneous Addison’s disease, probably because in the former replacement therapy had been given from the start, without a period of chronic adrenal insufficiency intervening. The glucose tolerance test often gave abnormal results, showing both increased and reduced tolerance even in patients who, from clinical appearances, were apparently receiving adequate steroid therapy. Of fifteen totally adrenalectomized patients, three showed diabetic blood sugar curves and one developed frank diabetes mellitus later: the reasons why cortisone in such patients may be particularly diabetogenic are discussed. On the other hand “hypoglycaemia unresponsiveness” was more common. The water-excretion test of Kepler also gave evidence of adrenal insufficiency in all cases, in spite of clinically adequate steroid replacement therapy. Excessive weight gain was noted to be a sign of cortisone overdosage in some cases, and was due to obesity following excessive food intake as a result of markedly increased appetite.

The question of adrenal regeneration is discussed at length and it is concluded that probably as little as 2 to 3 per cent. of the total adrenal tissue may secrete half the basal hormone requirement in the absence of stress. But even with clinically adequate maintenance treatment, signs of adrenal insufficiency can still be detected by laboratory tests, and the authors conclude that there is no really physiological dose of cortisone. No difference
appears to exist between the adrenal insufficiency of spontaneous Addison’s disease and that which results from adrenalectomy.

Kenneth Gurling.


The aim of these studies was to determine whether the production of aldosterone-like steroids by the adrenal cortex is necessarily associated with production of hydrocortisone-like steroids, whether exogenous ACTH increases the production of aldosterone, and lastly whether this production is diminished by suppression of endogenous ACTH. They were carried out at the National Heart Institute, Bethesda, Maryland, on 23 subjects, including ten healthy adults, seven patients with heart failure, three with cirrhosis, and one each with nephrosis, hypopituitarism, and amyloidosis, in whom the effects of low- and high-sodium diets and of ACTH administration were studied with reference to urinary excretion of 17-hydroxycorticoids and aldosterone.

In all subjects sodium restriction led to increased aldosterone output, while an abrupt change from a low to a high sodium intake (over 100 mEq. a day) resulted in a fall in aldosterone excretion; hydrocortisoid excretion was not affected. In patients with oedema due to congestive heart failure or other cause, hydrocortisoid excretion was normal, but the urinary aldosterone level was raised. ACTH given intramuscularly or intravenously, whether the subject was receiving a high- or low-sodium diet, produced a tenfold rise in hydrocortisoid excretion and a twofold rise in that of aldosterone. The increase in aldosterone excretion was of brief duration, however, lasting for only 2 to 4 days even during continuous stimulation with ACTH, and aldosterone excretion eventually fell below the initial level, probably because of excess production of sodium-retaining corticoids at the same time. Administration of suppressive doses of cortisone (of the order of 200 mg. a day) did not depress aldosterone output, suggesting that ACTH does not mediate in its liberation and indicating that excess of sodium is a more potent inhibitor.

Although the patient with hypopituitarism showed reduced hydrocortisoid excretion and a slow response to ACTH, there was no impairment of aldosterone excretion and sodium conservation was normal. Thus aldosterone secretion appears to be controlled by various factors, including loss of extracellular fluid, potassium loading, diseases such as congestive heart failure, and, to a small extent, ACTH. This is not the case with cortisone derivatives. The authors conclude that the “unitarian” hypothesis of the sole control of adrenocortical function by pituitary adrenocorticotropic hormone is untenable and that a dual mechanism involving the anterior pituitary gland and changes in body fluid and electrolyte content must be assumed, the latter changes having little or no effect on the secretion of hydrocortisone.

[Detailed figures of steroid levels are not given in the text, but are indicated in the figures accompanying the paper.]

Kenneth Gurling.


At S.N. Medical College, Agra, the authors have studied the evolution of hepatic cirrhosis, the possibility of its reversal, and the effect of cortisone on the cirrhotic process. In 300 young albino rats of both sexes cirrhosis was induced by means of twice-weekly subcutaneous injections of 0.1 ml. carbon tetrachloride per 100 g. body weight in an equal volume of light liquid paraffin; after the 3rd week seven to nine of the rats were killed at weekly intervals 60 to 64 hours after the last injection. From the 6th week onwards batches of eight rats were given further injections, four of these animals being then killed after 2 weeks and the other four after 3 weeks, in order to study the “reversibility” (defined as appreciable recession in a maximum of 3 weeks) of the cirrhotic process. At necropsy the livers were resected, slices of hepatic tissue fixed in 10 per cent. formalin, and stained with haematoxylin, eosin, Masson’s stain for connective tissue, and Gomori’s stain for reticulum; samples were also minced for estimation of the collagen content by the method of Lowry. Both adrenal glands were examined for ascorbic acid content and sudanophilia, stained sections of the cortex examined histologically, and histochemical estimations made of the 17-ketosteroid content. Adrenal function was further studied by exposing two animals in each experimental group to the stress of cold by putting them on ice for 3¹/₄ hours, while two others in each group received subcutaneous injections of histamine (1-0 mg.) and corticotropin (1-0 mg.). The control group consisted of thirty rats which were killed at intervals of from 3¹/₂ to 60 hours after injection of the carbon tetrachloride and of four rats which were exposed to stress as above without previous injection. The severity of the cirrhosis was assessed in five arbitrary grades depending on the thickness and extent of the reticular trabeculae and the degree of pseudolobulation (the five grades are illustrated in the photomicrographs which accompany the paper).

The results were as follows: Normal animals exposed to stress or a single injection of carbon tetrachloride showed depletion of the ascorbic acid level in the adrenal glands, indicating activation of the cortex. Subsequently this value returned to normal levels or beyond, the latter stage representing relative inactivity. The cirrhotic process could be divided into four phases: in Phase I (up to the 5th week) there was little change in the liver reticulum, and the ascorbic acid levels in the adrenal glands were high. In Phase II (6 to 9 weeks) there was cellular fibrosclerosis, which, however, was not reversible, and the adrenal ascorbic level was low, indicating activity; at this stage the adrenal glands could be depleted by stress. Phase III (9th to 11th week) marked the beginning of irreversible cirrhosis, in which the adrenal ascorbic acid levels were slightly lowered or normal; here depletion under stress was incomplete. In Phase IV the cirrhosis was irreversible and progressive:
the adrenal ascorbic acid levels were high and depletion under stress was reduced, the depletion effect of histamine being greater than that of corticotrophin, suggesting some changes at both the pituitary and adrenocortical levels.

After discussing the various mechanisms involved in these reactions, the authors conclude that the reversible stage of cirrhosis is associated with normally functioning adrenal glands, or glands which can still respond by showing further activity when exposed to stress. Irreversible cirrhosis is associated with functionally damaged adrenal glands.

In the second part of this study albino rats were given carbon tetrachloride as above. From the 8th week onwards batches of six rats were isolated each week and given no more carbon tetrachloride, but instead each received a daily intramuscular injection of cortisone acetate as follows: 5 mg. per day for 6 days, 10 mg. per day for 3 days, and finally 5 mg. per day for 2 days; 3 days after completion of these injections the experimental animals were killed and they and the control animals examined as in the first part of the study. The results showed that cortisone assists in the regression of hepatic cirrhosis only during the period in which the condition is naturally reversible, but that the hormone has no effect on the later irreversible stages once "mature fibrous tissue" has been laid down. B. G. Maegraith.


A 49-year-old woman with lupus erythematosus disseminatus treated with ACTH presented pronounced retinal changes similar to thrombosis of the central retinal vein. In a 38-year-old woman with a similar disease receiving similar drugs, the blood-pressure rose and she showed increasing fundus changes of a hypertensive character and myopia. A 43-year-old woman with chronic polyarthritis suffered a retinal haemorrhage and slight increase in myopia during treatment with ACTH. A 70-year-old woman with polyarthritis showed macular oedema during such treatment. G. von Bahr.


Corrigendum

In the article by Dr. J. Rotés-Querol entitled "Osteo-articular Sites of Brucellosis", which appeared in the March issue of the Annals (1957), 16, 63, col. 2, line 33, for 'Osteophytes' read 'Osteo-articular sites'.