

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


A follow-up study was carried out during 1953 on 1,540 patients out of about 4,000 who had been admitted to Malmö General Hospital, Sweden, with rheumatic fever or some other manifestation of acute rheumatism, heart disease of presumed rheumatic origin, acute nephritis, or congenital heart disease during the years 1930-50. An analysis of data derived from these patients and from the records of about 500 others who had died in the meantime was made with particular reference to the natural history of rheumatic heart disease and the possibility of its prevention.

Of the 467 cases in which a definite diagnosis of rheumatic fever had been made originally, valvular disease was present at the time of follow-up in 25 per cent.; of 227 in which a diagnosis of “rheumatic fever (uncertain)” had been made, valvular disease was present in 11 per cent.; and of 51 patients with the original diagnosis of chorea (with no other rheumatic manifestation), 33 per cent. had valvular disease. Among the 120 cases of erythema nodosum and 311 of acute nephritis studied, the incidence of heart disease was so low that it is concluded that in these conditions no prophylactic measures against its development are necessary. There was a high incidence of recurrence among the patients with definite rheumatic fever and chorea, and the higher incidence of heart disease in patients who had had several attacks clearly indicated the need for prophylaxis against recurrence. First attacks were by no means confined to childhood, as in 124 out of 467 cases of definite rheumatic fever the patient was aged between 20 and 29 years old at the onset. There was a higher incidence of valvular disease in general in females than in males, although pure aortic lesions were far commoner in males than females.

It is suggested that there are four strategic points at which the attack on rheumatic heart disease should be concentrated:

(1) adequate treatment of the first attack of acute rheumatism;
(2) the prevention of recurrences;
(3) the medical control and supervision of patients with “possible” and “potential” heart disease; and
(4) the recognition of the correct time for surgical treatment.

[This paper contains much valuable statistical information which is difficult to abstract.] C. Bruce Perry.

Treatment of Acute Rheumatic Carditis with Prednisone. (La terapia delle car diiti reumatiche evolutive con prednisone.) Casolo, G., Di Nardo, A., Maggi, C. A., Orcese, L., Zanazzi, A., and Ciafaloni, D. (1955). Minerva med. (Torino), 2, 33. 12 figs, 16 refs. Prednisone (Metacortandracin) was used at the Ospedale Maggiore, Milan, in the treatment of fifteen patients [ages not stated] with well-defined rheumatic carditis, which was classified as “acute” in ten cases and “subacute” in five. Severe cardiac decompensation was present in three of the acute cases, and pancarditis in one. Antibiotic and cortisone treatment had been unsuccessful and in some cases had even aggravated the carditis. Metacortandracin was given by mouth three or four times daily in a total dosage of 30 to 40 mg. (except in two cases in which 50 mg. was given). The treatment was continued until the clinical and laboratory findings were normal or near normal, which occurred after 8 to 15 days’ treatment in all but three cases, in which progress was delayed and treatment carried on for 30 to 40 days. All the patients responded well, and the more acute the condition, the greater was the therapeutic effect. The fact that the drug was so well tolerated permitted the use of large doses in two special circumstances:

(1) in controlling the recurrence of acute cardiac symptoms following a too rapid diminution of the dosage; and
(2) in preparation for tonsillectomy.

The side-effects were slight and the damaging influence on the cardiac condition of the disturbance of water and electrolyte metabolism which frequently accompanies
cortisone therapy was absent. Within the limits imposed by the small number of cases treated and the short period of observation (80 days), these results indicate that Metacortandracin is a drug of real value in the treatment of rheumatic carditis.

[It is impossible to do justice in an abstract to this well-documented paper, which should be read in the original by those interested.] V. C. Medvei.


The authors argue that mitral valvotomy will not improve the condition in cases of rheumatic mitral stenosis in which myocardial insufficiency resulting from the rheumatic process rather than mechanical narrowing of the valvular orifice is the predominant cause of circulatory dysfunction. In support of this view they report the findings in sixteen patients with mitral stenosis studied at Columbia University and Bellevue Hospital, New York. These patients could be divided into two distinct groups:

The first group of eight patients gave a history of almost constant, progressive disability; haemodynamic investigation showed moderate to severe pulmonary hypertension and either a low or normal cardiac output, with diminished blood-flow response during leg-exercise. In these cases mechanical block at the mitral valve was the predominant cause of dysfunction; at surgery no mitral valve admitted the tip of the index finger. After the performance of valvotomy the pulmonary pressure fell to a greater or lesser extent, both at rest and during exercise, in every patient and the pulse pressure decreased.

The eight patients in the second group gave a history of occasional complete incapacity, but with relatively asymptomatic intervals. The haemodynamic findings showed that pulmonary tension at rest was normal or but little raised (except in one case first seen in heart failure), but that during exercise two patterns of response were found in the pulmonary circulation, namely, very little increase in pulmonary arterial pressure in two cases and a sharp rise in five cases. Analysis of the total findings in this group suggested that myocardial insufficiency unrelated to mechanical obstruction was the predominant lesion in these cases. This was partially confirmed by the fact that the performance of valvotomy in two of them was ineffective.

The authors suggest that it would seem logical to insist on a demonstration of the presence of pulmonary hypertension in every candidate for the operation of mitral valvotomy.

R. S. Stevens.


Under the name of "subacute polyarthritis of adults" the authors include a number of diseases of obscure aetiology, the salient features of which are a vagrant polyarthritis of exudative type, with remittent pyrexia. In general, infective polyarthritis, which responds to treatment with antibiotics, and rheumatic fever, which responds to salicylates, can readily be recognized, but in this communication from Montpellier the authors describe five borderline cases in which there was a febrile polyarthritis resembling one or other of these types, but which was resistant to both antibiotics and salicylates, although all five were promptly controlled by cortisone. These cases bore little or no resemblance to classic rheumatoid arthritis.

One of these cases, which resembled an infective polyarthritis, is described in detail. It occurred in a female patient aged 27 who a few days after an attack of pharyngitis developed pyrexia and polyarthralgia, which proved to be completely resistant to antibiotics and massive doses of salicylates. A few days after the onset a scarlatiniform eruption developed, followed by desquamation. There was a marked albuminuria, which cleared up later without any signs of renal damage. The administration of cortisone brought prompt subsidence of the signs and symptoms within a few hours; maintenance doses of the hormone were continued for 4 months, and the patient has remained well for a year.

In three other cases the symptoms closely resembled those of rheumatic fever, the heart being involved in one case, but all differed in being completely unaffected by salicylates. In all three cases there was a spectacular response to cortisone, and maintenance treatment for some months appeared to bring lasting cure.

Kenneth Stone.


From the results of a previous study (Amer. J. Med., 1954, 16, 168; Abstracts of World Medicine, 1954, 16, 320) the authors came to the conclusion that in the acute stage of rheumatic fever there seems to be no definite advantage as between treatment with aspirin, cortisone, or corticotropin (ACTH). Of the patients included in that investigation at Warren Air Force Base Hospital, Wyoming, 128 have now been followed up for 14 months from the beginning of treatment. Of these, 52 had been treated with aspirin, and 38 each with cortisone and ACTH respectively; the patients were also given prophylactic doses of penicillin and sulphonamides, and received a low-salt diet supplemented with potassium chloride. [The fact that the patients were young men and that nearly all of them were treated early in the course of a first attack of rheumatic fever should be emphasized.]

Analysis of the results showed that cortisone appears to have a slight but definite advantage over the other two drugs in respect of the long-term results. Thus, in the cortisone-treated group significant murmurs were present in only about seven out of 38 patients (18.4 per cent.) at the end of 14 months as compared with 34.2 and
34.6 per cent. in the other two groups. Moreover, murmurs did not develop so frequently during treatment with cortisone, and when they did they disappeared more often by the end of the period of therapy. Also, the number of murmurs that disappeared between the end of treatment with cortisone and the fourteenth monthly assessment was greater than with ACTH or aspirin. Lastly, no aortic diastolic murmurs were present at the end of 14 months in the cortisone-treated group but persisted in four of those given aspirin and in one patient given ACTH. In general, all the patients did well, and although the results obtained with cortisone were slightly better than those obtained with aspirin or ACTH the authors consider that this finding needs confirmation by further and longer-term studies.

A. Paton.


Despite the publication of many reports on the use of cortisone in acute rheumatic carditis, agreement as to its role in the prevention of residual cardiac damage is far from general. This paper from the Children's Hospital of the University of Pittsburgh reports the findings in a series of 53 children treated for an initial attack of rheumatic carditis with large doses of cortisone for various periods (usually 6 weeks) and followed up for periods ranging from 1 to 39 months [but with no control series treated by other means], two being retreated for recurrent attacks. The ages of the children ranged from 3-9 to 15-4 years. The diagnosis was established according to the criteria of Jones, but any case in which the clinical diagnosis of endocarditis was in the least doubtful was omitted from the analysis. In all 55 attacks, carditis was present at the onset; cardiac enlargement was present in thirty of the 55 and the mitral valve was affected in 95 per cent. of the attacks, particularly in those cases in which treatment was started 6 or more weeks after the onset. Most of the patients received 300 mg. cortisone a day by mouth for 6 weeks (though the period of treatment ranged from 3 to 113 days), the dosage then being gradually reduced over a period of 2 weeks. Treatment also included bed rest, low-salt diet (2.5 to 10 mEq. sodium with 150 mEq. potassium daily), penicillin, and digitalis or other drugs as necessary for heart failure. There were two deaths in the series. Hypertension was troublesome in two cases and treatment had to be stopped in one case because of toxic psychosis, from which the patient recovered. The authors conclude that this regimen is relatively safe and consider that its application in these cases prevented and reduced the incidence of clinically recognizable cardiac abnormalities. [It is not clear on what evidence this conclusion is based.]

The laboratory findings in this series are described in the second part of the paper. During sixteen of the 55 attacks B-haemolytic streptococci were isolated from the nasopharynx despite prophylactic penicillin therapy (100,000 units by mouth three times a day between meals), but there were no accompanying symptoms or rise in antistreptolysin-O titre. Comprehensive haematological and biochemical investigations were performed, but apart from mild hypochloraemic alkalosis no abnormality attributable to the treatment was detected, the regimen being well tolerated by the majority of the patients.

E. G. L. Bywaters.


It frequently happens that a history of rheumatic fever cannot be obtained in patients suffering from rheumatic heart disease: yet the recognition of rheumatic carditis is of obvious importance. From their experience at the Xth District Paediatric Hospital, Budapest, the authors suggest two radiological methods which they have found of diagnostic value in such cases:

The first is screening of the heart for signs of left auricular dilatation; this is best seen on turning the patient through 70° to the left while barium is present in the esophagus.

The second sign is failure of the cardiac silhouette to become smaller on performance of Valsalva's manoeuvre. The latter procedure is possible in young patients from the age of 6 years, and the authors state that holding the breath in deep inspiration for a few seconds is sufficient.

On examination of 175 [the summary speaks of 178] children thought to be suffering from rheumatic carditis but with few or no symptoms 24.5 per cent. showed left auricular dilatation and 21 per cent. a positive result in the Valsalva manoeuvre, while both signs were present in 33.6 per cent. In contrast neither sign was observed in any of 200 children without carditis who were examined as a control. The authors suggest that the presence of either sign is good evidence in favour of active carditis, but that the absence of either does not exclude the possibility of carditis.

F. Storer.


In the first part of this study investigations were carried out on thirty children with Sydenham's chorea at Salt Lake City County Hospital (University of Utah), in an attempt to confirm the presence of abnormal adrenocortical function by means of serum assays of various substances. It was found that there was occasional elevation of the serum mucoprotein and hexosamine levels, and that the level of the serum non-glucosamine polysaccharides was consistently elevated. The plasma levels of 17-hydroxyxycorticosteroids were generally low, while the endogenous corticotrophin level was usually high. It is suggested that these last two findings taken together indicate relative adrenocortical deficiency. Nevertheless the plasma 17-hydroxycortico-
ACTH, so that the adrenal glands were still capable of further activity under sufficient stimulus.

In the second part of the paper the results of hormone therapy in thirteen attacks of chorea in eleven patients (six boys and five girls) are described. ACTH was given to nine patients in doses of 2 to 4·4 units per kg. body-weight per day, administered 6-hrly, and cortisone to two patients in doses of 7·25 to 12 mg. per kg. bodyweight per day. All but one of the patients received in addition large doses of ascorbic acid and prophylactic penicillin, and were kept at rest in bed. The duration of treatment was from 18 to 80 days. The eleven case histories are presented in detail. In five cases the response was dramatic; before treatment, two of these patients had been stuporous with severe symptoms of encephalitis and yet 3 days after treatment was begun they could feed themselves, speech became normal, and they could even walk. In five other cases marked improvement was obtained. Only one patient failed to respond and this was the patient who had received no ascorbic acid. No attempt was made to assess the benefit of treatment on the ultimate carditis.

This almost completely successful effect of hormonal treatment of Sydenham’s chorea is in direct contrast to the results reported by workers in Great Britain, for example, by Bywaters (Arch. Dis. Childh., 1952, 27, 161.) G. S. Crockett.

Cortisone and ACTH in the Treatment of Chorea Minor.
(II cortisone e l’ACTH nella cura della corea minor.)

The treatment is described from the Univeristy Clinic for Nervous Diseases, Padua, of thirteen cases of chorea minor (Sydenham’s chorea) with cortisone and ACTH (corticotrophin). Brief case histories are given of all the patients, who ranged in age from 6 to 16. The dose of cortisone was 5 to 7 mg. per kg. bodyweight and of ACTH 2 to 3 mg. per kg. daily, this being divided in the first few days of treatment into 6-hrly doses but subsequently given 12-hrly. [The choice between cortisone or ACTH for the treatment of any particular patient appears to have been made at random.]

In eleven of the patients a complete recovery was recorded within one to 2 weeks, in some cases being dramatically rapid. It was found, however, that it was only a symptomatic relief and that relapse tended to occur unless the administration of the drug was continued for a considerable time. The therapeutic background of the treatment of chorea is discussed at length, and the authors conclude that these hormones constitute a considerable advance in the treatment of chorea minor.

Donald McDonald.


At Johns Hopkins Hospital, Baltimore, 146 children aged from 3 to 14 years who fulfilled the criteria for the diagnosis of rheumatic fever or rheumatic heart disease were studied as out-patients for periods of from 3 to 18 months (average period 13 months). One group of 82 patients (Group I) was instructed to take one tablet of 200,000 units benzathine benzylpenicillin by mouth each morning, and the remaining 64 (Group II) took 0·5 or 1·0 g. “Sulfose”, a preparation containing equal parts of sulphadiazine, sulphanerazine, and sulphamethazine, the smaller dose being prescribed for children weighing less than 60 lb. (27·2 kg.). Each child was examined once a month, when throat swabs were taken and antistreptolysin-O (AS-O) titres and sedimentation rates were estimated, blood counts determined, and blood films examined.

During the period nine children developed recurrence of rheumatic fever, four in Group I and five in Group II. In eight of these cases there was an associated rise in the AS-O titre; the ninth patient gave a history of an upper respiratory infection and a Type 18 streptococcus was isolated from the throat. In each treatment group eleven children (22 in all) showed a rise in AS-O titres without developing a rheumatic relapse. In the penicillin-treated group, Group-A streptococci were isolated from the throats of fifteen, of whom eight showed a rise in AS-O titre and the other seven were considered to be carriers. In those receiving the sulphonamides Group-A streptococci were isolated from the throats of seventeen; in seven of these there was a rise in AS-O titre and the remaining ten were presumed to be carriers. Of the 82 patients taking penicillin, two developed urticarial rashes, but one was able to continue with the treatment. Toxic effects were noted in seven children in Group II; one of these had recurrent haematuria and six developed varying degrees of leucopenia, in some instances after a period of 4 to 8 months’ treatment.

It is concluded that oral administration of 200,000 units benzathine benzylpenicillin is as effective as sulphonamides as a prophylactic agent in rheumatic fever and is less toxic.

C. Bruce Perry.


The authors report from the University of Rochester School of Medicine, Rochester, New York, the results of the treatment of 1,175 proved cases of β-haemolytic streptococcal infection in children with a single intramuscular injection of 600,000 units benzathine benzylpenicillin. The series included 944 cases of sore throat, 156 cases of scarlet fever, seventeen of otitis media, five of sinusitis, twenty of cervical adenitis, four of skin infection, eighteen of miscellaneous conditions, and eleven carriers.

In the majority of cases the infection was promptly and permanently cleared, but a number of recurrences or development of the carrier state appeared within 2 months, 8·3 per cent. with a different type of organism and 6·0 per cent. with the same type. Throat swabs
became negative one day after treatment in 76 per cent. and in 95 per cent. at the end of a week. No evidence of subsequent rheumatic fever or definite evidence of acute nephritis was observed, although one child developed transient albuminuria and haematuria. The erythrocyte sedimentation rate was raised in 14 per cent. of 664 cases tested between the second and fourth week and in 19 per cent. of 79 cases examined after the fourth week. Varying degrees of pain or discomfort at the site of the injection was the commonest untoward reaction. In 100 specially studied cases there were two cases of urticaria. The blood levels of penicillin attained by this method of treatment were never very high and indeed often proved inadequate for the treatment of deep-seated lesions, such as streptococcal cervical adenitis. However, it is claimed that in 94 per cent. of patients the infection was promptly cured and followed by no recurrence or complication. C. Bruce Perry.


In this comparative study of the effects of different treatment regimens, reported from the University of Utah College of Medicine, Salt Lake City, eighty children aged from 3½ to 15 years with acute rheumatic fever were divided into four groups:

(1) 32 were treated with ACTH in doses of 2 to 3.74 units per kg. bodyweight intramuscularly daily; these children also received 500 mg. ascorbic acid daily;

(2) Fourteen children were given cortisone either intramuscularly or orally in doses of 3 to 9 mg. per kg. body weight per day every 4 or 6 hours. In both these groups the initial dose was continued until all acute symptoms disappeared, the serum mucoprotein level showed a marked decrease, and the erythrocyte sedimentation rate (E.S.R.) had been less than 20 mm. in one hour for 3 to 5 days; the daily dose was then gradually reduced;

(3) 21 patients were treated with salicylates in doses of 9 to 3 grains (45 to 200 mg.) per kg. bodyweight per day at 4-hrly intervals; this dosage was continued for varying times, but in the majority until the E.S.R. had been normal for at least 8 days;

(4) Lastly, thirteen patients were treated by rest in bed alone.

The age range and the duration of symptoms before the start of treatment were similar in all four groups. In all but one child (treated by rest in bed alone) there was clinical evidence of carditis, with the development of new murmurs at the beginning of treatment.

The mean duration of joint pains in the three groups given drugs was 1.7, 2, and 3.3 days respectively, and 19-8 days in those treated with bed rest alone. The mean number of days until the E.S.R. fell to normal was respectively 15-6, 11-9, 43-4, and 48-2. Rebound phenomena on stopping treatment were observed as follows:

Two out of 28 patients receiving ACTH developed arthritis or arthralgia, three fever, and seventeen a raised E.S.R.;

Of twelve treated with cortisone, two exhibited arthralgia, four fever, and six a raised E.S.R.;

Of 21 receiving salicylates, arthritis or arthralgia was noted in seven, fever in six, and a raised E.S.R. in eight.

On discharge, persistent cardiac murmurs were present in 47 per cent. of the children treated with ACTH, 64 per cent. of those treated with cortisone, 76 per cent. of those given salicylates, and 69 per cent. of those treated with bed rest alone.

However, in those cases followed for 12 months, cardiac murmurs persisted in four out of 23 in the ACTH group, in one out of eight in the cortisone-treated group, in fourteen out of nineteen given salicylates, and in seven out of thirteen treated by bed rest.

Further, after 3 years the corresponding figures were one out of sixteen, none out of one, ten out of eleven, and four out of thirteen in the respective groups. During the 3 years follow-up new murmurs developed in three of the ACTH-treated cases, one of the cortisone-treated cases, fourteen of those given salicylates, and four of those treated by bed rest. [These figures are difficult to understand and suggest that there must have been an undue number of recurrences in the two groups of patients not treated with hormones.]

Of the patients lost to follow-up, approximately 25 per cent. of the ACTH group, 50 per cent. of the cortisone group, 90 per cent. of the salicylates group, and 71 per cent. of the bed-rest group had murmurs at their last examination.

It is concluded, despite previous reports to the contrary, that when given in adequate doses (at least 2-4 units ACTH or 6-6 mg. cortisone per kg. bodyweight a day) these hormones are of value in reducing the incidence of permanent cardiac damage in patients with rheumatic fever. C. Bruce Perry.


Since methods are now available, by the use of chromatographic separation and infra-red analysis, for identifying the major components of purified urinary 17-ketosteroid extract, and since there is some evidence that the urinary 17-ketosteroids vary qualitatively in certain diseases, the author undertook the present investigation at New York Hospital-Cornell Medical Center, New York, to determine whether there is any such qualitative change in rheumatic fever. For this purpose 24-hr specimens of urine were obtained from four non-rheumatic children, four whose rheumatism was in an inactive phase, and two with active rheumatic carditis, in one before and one during ACTH therapy. All were between the ages of 6 and 10 years.

The technique of steroid analysis is laborious, and this study was limited to the α ketosteroids. Moreover, the analytical methods were applied to 5-mg. specimens of ketosteroids (and it is therefore not surprising that of
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the 35 reported \( \Delta \) ketosteroids which have been isolated from larger specimens (50 mg.), only a few were here identified. However, the limited results obtained suggest, nevertheless, that there is no qualitative difference between the urinary ketosteroids of rheumatic and non-rheumatic children. But in the patient with active rheumatic carditis who was receiving ACTH both quantitative and qualitative differences were observed; included among the abnormal steroids in this case was one of unknown structure similar to that found by other investigators in the urine of patients with adrenal hyperplasia.

[The author stresses that this small-scale study was designed mainly to assess the possible value of a larger investigation, and is presented as a preliminary report.]

Kenneth Stone.


The authors have investigated at the University of Utah College of Medicine, Salt Lake City, the plasma levels of circulating adrenal steroids in patients with rheumatic fever who were being treated by bed rest alone or with cortisone, ACTH, or salicylates. Serial measurements of the concentration of 17-hydroxycorticosteroids (which includes 17-hydroxycorticosterone) in the plasma were made by the method of Nelson and Samuels (J. clin. Endocrinol., 1952, 12, 519). In the cases given hormones blood samples were obtained 4 to 5 hours after administration of one dose and just before the next was due.

In the group of nine patients treated by bed rest alone, the mean plasma steroid level was lower than the mean normal value, and a similar decreased level was found in the eight patients treated with salicylates. In the 46 patients receiving cortisone orally or lyophilized ACTH intravenously the plasma steroid levels were inconstantly elevated during the period of maximum therapy. But in the group of eleven patients receiving cortisone or ACTH gel intramuscularly, elevation of plasma steroid level was constant. Since the clinical response to the hormones, however administered, was equally satisfactory, the authors suggest that such response is not dependent upon sustained elevation of the plasma steroid level.

Kenneth Stone.


In view of the observation of a significant increase in urinary coproporphyrin excretion in patients with rheumatic fever reported by Kapp and Coburn (Brit. J. exp. Path., 1936, 17, 255) the authors carried out a study of coproporphyrinuria, with observations on free erythrocyte porphyrins, in fifteen children with acute rheumatic fever and fifteen comparable controls at the Doernbecher Memorial Hospital for Children (University of Oregon), Portland, Oregon, the results of which are here presented.

They confirmed the earlier observations that there is a significant increase in daily excretion of this urinary pigment in all rheumatic fever patients, and that in both rheumatic and normal children the coproporphyrin is predominantly of the Type III isomer.

They found a direct correlation between urinary coproporphyrin excretion and body weight in normal children, and the correlation still held for the increased values occurring in rheumatic fever. The excretory level of the pigment was not affected by the administration of salicylates in non-toxic doses.

The erythrocyte protoporphyrin and coproporphyrin values in rheumatic fever were normal, and there appeared to be little evidence of alteration in porphyrin metabolism in the bone marrow. The liver, however, synthesizes a number of plasma constituents which present characteristic changes in acute rheumatism; among these are the serum mucoproteins. In this study the serum mucoprotein level was well above normal in all the patients with rheumatic fever, but the values returned to normal during convalescence, accompanied by a decrease in the coproporphyrinuria. The authors suggest that the liver is the source of the Type III coproporphyrin in the urine in acute rheumatism.

Kenneth Stone.


Prophylactic injections of benzathine benzylpenicillin were given to children attending the out-patient clinic at Irvington House, New York, who had had an attack of rheumatic fever within the preceding 18 months. Between September, 1952, and August, 1954, 145 children aged 6 to 16 years each received an intramuscular injection of 1,200,000 units benzathine penicillin once a month for a total of 2,193 patient months, an average of about 20 months per patient. A further 265 patients in hospital in the acute or convalescent phase of rheumatic fever were similarly treated. The incidence of haemolytic streptococcal infection and the frequency of recurrence of rheumatic fever were compared with similar figures for a group of children treated at another hospital with penicillin by mouth or sulpha-diazine.

There were no recurrences of rheumatic fever in the 145 out-patients given intramuscular injections of benzathine penicillin. In the group of 111 patients given penicillin by mouth there were two recurrences and in the groups of 73 given sulpha-diazine there were five. From the patients treated with benzathine penicillin throat swabs were taken each month and cultured; only three cultures were positive for haemolytic streptococci (two of these were from the same patient at different times). One patient from whom a positive culture was obtained developed clinical pharyngitis. During the same period 52 (19.3 per cent.) of 269 untreated control children from the same environment were found to be harbouring Group-A haemolytic streptococci. Positive cultures were
obtained from throat swabs from thirteen of 99 children treated with penicillin by mouth and from eight of the 73 given sulphadiazine. Estimation each month of the serum antistreptolysin-O titre in the patients receiving benzathine penicillin revealed a significant rise in only three; in two of these there was no other evidence of streptococcal infection.

For a study of toxic reactions to intramuscular injection of benzathine penicillin the hospital patients were grouped with the out-patients, giving a total of 4,871 injections in 410 patients. Most of the patients experienced muscle soreness and tenderness for 1 to 3 days, associated in about 10 per cent. with low-grade fever for 24 to 48 hours. Urticaria was noted in four patients but this was transient and did not interfere with treatment. Various non-streptococcal infections (mainly of the upper respiratory tract and skin) occurred, and in two patients bacterial endocarditis due to Streptococcus viridans developed (in one case following tooth extraction).

It is concluded that single monthly injections of 1,200,000 units benzathine benzylpenicillin confer a high degree of protection against infection with Group A haemolytic streptococci and against recurrences of rheumatic fever. C. Bruce Perry.


The authors have used the new synthetic steroid Metacortandracin in the treatment of some twenty patients, the majority of whom were suffering from rheumatic fever. Analysis of the clinical response and results of laboratory tests showed that a daily dose of 10 to 50 mg. of the new drug was as effective as a larger dose of cortisone and produced fewer side-effects. It differs from cortisone in certain details in its action on vitamin-C metabolism. They also found the drug valuable in a case of bronchial asthma and another of pollen allergy. L. Michaelis.


The authors describe two cases seen at the University Medical Clinic, Frankfurt-am-Main, which illustrate the danger of hormone therapy in the presence of streptococcal infection. Both patients had rheumatic fever, with tonsillitis, and in both the administration of ACTH (corticotropin) controlled the polyarthritis for a time. An acute exacerbation then took place in the tonsillitis and the condition of the joints relapsed once more. Antibiotics usually clear up an attack of tonsillitis very quickly, but failed to do so in these patients, even in high dosage. Evidence of cardiac damage was present in both cases.

The authors stress that in cases of acute rheumatism antibiotic treatment for associated tonsillitis should be carried out as early as possible, and if the throat infection persists tonsillectomy should be considered; it may thus be possible to avoid this particular complication of hormone therapy. In three other cases observed at the same time the tonsillitis had completely subsided before treatment with ACTH was begun and in these cases no complication was encountered. David Preiskel.


Chronic Articular Rheumatism
(Rheumatoid Arthritis)


The clinical records and the results of a follow-up investigation of 72 children (30 males and 42 females) with rheumatoid arthritis admitted to the Royal Hospital for Sick Children, Glasgow, since 1930 are reviewed. In thirty cases the age at onset of the disease was 5 years or less. The joint involvement was usually bilaterally symmetrical and muscle atrophy developed rapidly. Transient skin rashes were noted in eighteen cases and psoriasis was present in four others. Adenopathy developed in 36 cases during the illness, accompanied by
splenomegaly in ten. In five cases, two of which were fatal, there were features of both rheumatoid arthritis and rheumatic fever.

Of the 72 patients, 56 were traced, 49 of these being re-examined. The disease was quiescent—that is, there had been no joint pain and tenderness for at least 2 years—in 34 patients. Of these, 22 made a complete recovery, five were moderately crippled, five severely crippled, and two were only mildly disabled.

The value in treatment of ACTH, cortisone, vitamin D₃, gold injections, salicylates, and tinsulocorticoids is discussed; it is concluded that recovery is not related to any particular form of treatment given. Kathleen M. Lawther.


A further study of the long-term treatment of rheumatoid arthritis with cortisone is presented from Rigs hospitalet, Copenhagen, with special reference to adrenocortical activity after such treatment. The series studied consisted of fifty cases of rheumatoid arthritis in fifteen males and thirty-five females ranging in age from thirty to fifty years. The more severe type of case preponderated. Treatment was initiated with ACTH (coricetropin) in order to determine the initial 17-ketosteroid excretion rate, and was then continued with cortisone [presumably by mouth] at a maintenance dosage of 50 to 75 mg. daily, the level being determined by the patient's tolerance rather than by remission of symptoms. All other treatment was discontinued and the use of analgesics was avoided as far as possible.

In nineteen cases adrenocortical function was re-assessed after 9 to 41 months of continuous cortisone therapy by determining the rate of urinary excretion of 17-ketosteroids following the administration of ACTH in doses of 20 units 6-hrly. Before treatment the average increase in 17-ketosteroid excretion was 100 per cent. During treatment the average basal rate of excretion fell by 40 per cent., but stimulation with ACTH after a long period of cortisone therapy resulted in a rise in 17-ketosteroid excretion to an average of 420 per cent. of the pre-stimulation value, and 250 per cent. of the pretreatment value. The mode of response after cortisone therapy varied, the patients falling into three groups according to the rapidity of the response, but the type of response appeared to be unrelated to age, sex, clinical condition, or dosage and duration of cortisone therapy. The decrease in adrenocortical function induced by prolonged cortisone therapy is therefore shown to be readily reversible on stimulation with ACTH.

From the clinical aspect, complete remission was induced in three cases, "considerable improvement" in nineteen cases, "some improvement" in fifteen, and none in thirteen patients. In sixteen of the fifty cases treatment was discontinued on account of an unsatisfactory response or the development of complications. Of the remaining 34 patients, the number totally incapacitated fell from eight to one, while the number of those able to work increased from two to 21. Some undesirable side-effects were noted in practically all cases. Mental disturbance occurred in eleven patients, but with no permanent damage. Two cases of gastric ulcer are recorded, and two deaths from pneumonia.

It is concluded that prolonged treatment with cortisone has proved of value in more than half the cases studied, and is indicated in cases where the disease progresses actively despite the application of other methods of control or in very active cases in order to inhibit progress before irreversible joint changes can occur. The patient should be kept continually under observation, and particular care taken to increase the dosage of cortisone rather than to stop treatment on the occurrence of infection, trauma, or acute surgical emergencies.

Harry Coke.


The author reports the results obtained in the treatment of 25 patients (eight male and seventeen female) suffering from rheumatoid arthritis with cachets each of which contained 6 mg. cortisone and 320 mg. sodium pyrocatechol-3-carboxylate; in all but one case not more than four cachets were given daily. [The patient's ages are not stated.] Before treatment the patients were classified by the grade of the arthritis and the degree of functional impairment according to the criteria of the International League against Rheumatism, and they were similarly re-assessed at the end of 17 months.

At that time four patients had had a remission and had stopped the treatment, in two cases medication had to be interrupted as the patients developed cholecystitis and gastric ulcer respectively, while in a further six cases the treatment was abandoned in view of the poor response to the low dose of cortisone employed. The results are analysed in a table, which shows that at the beginning of treatment the numbers of patients in Grades I, II, III, and IV were respectively nil, seven, fourteen, and four, while at the end of treatment the corresponding figures were twelve, eight, four, and one.

[A large part of this paper, which might well have been better devoted to giving a more detailed account of the present series of patients, is taken up in comparing the author's results with those recorded in two series reported in the U.S.A. in which no specific treatment was used, and with the report of the American Rheumatic Association on the use of cortisone. The figures quoted from these sources seem to support the author's claim regarding the superiority of the treatment employed in his own small series.] H. F. Reichenfeld.


The synthetic steroid prednisone ("Meticorten");
Metacortandracin was tried at the Beth Israel Hospital, New York City, in the treatment of twelve patients (three males and nine females, aged 35 to 63 years) suffering from active rheumatoid arthritis. The drug was usually given by mouth in a dosage of 30 mg. daily for at least 4 to 5 days until clinical improvement was observed, this being followed by gradual reduction over a period of 10 to 14 days to a maintenance dose of 5 to 20 mg. daily.

Complete remission was obtained in eight cases and major improvement in four. Within 24 hours of administration of the drug spontaneous joint pain disappeared and there was a diminution in articular and muscular stiffness. An increase in functional capacity and a reduction in the amount of joint swelling, local tenderness, and pain on movement were observed within a few days. In seven cases walking was improved. Electrolyte-balance studies revealed neither sodium retention nor potassium depletion. The antiarthritic effect of prednisone was considered to be four to five times that of cortisone or hydrocortisone.

Side-effects were minimal, transient, and reversible, the commonest being an increase in appetite (in eleven instances) with suppressive doses; some patients complained of insomnia and epigastric discomfort. There was no adverse change on metabolic activity.

Satisfactory results were also obtained with prednisone in systemic lupus erythematosus in a girl of 14 years and in acute gouty arthritis superimposed on chronic tophaceous gout in a man of 55. On the other hand, the drug had no effect on the rheumatic activity in a case of active rheumatic carditis. A. Garland.


Four groups of physicians working in separate clinics in Paris have recorded in this communication their results in a trial of the new synthetic steroid Metacortandracin in the treatment of a total of 65 patients with rheumatoid arthritis or ankylosing spondylitis.

(1) Coste and his colleagues treated six patients of whom five had already been receiving hydrocortisone. A placebo was given until a relapse occurred, when Metacortandracin was substituted. These workers conclude that rheumatoid arthritis of moderate severity can be relieved by Metacortandracin as effectively as by hydrocortisone, and that this relief is obtained with much smaller doses, namely, 30 mg. daily initially, later reduced to a maintenance dose of 15 to 20 mg. daily. No evidence was found in their patients of sodium retention, in spite of an average daily intake of 7 g. sodium chloride. One patient receiving 30 mg. Metacortandracin daily developed severe melancholia which, however, gradually cleared up when the dosage was reduced.

(2) de Séze and his colleagues treated 22 cases of rheumatoid arthritis and two of ankylosing spondylitis in patients most of whom had previously been treated with hormones for a considerable time, first with cortisone and then with hydrocortisone by mouth. In eighteen cases the disease had been fairly well stabilized by hydrocortisone, but activity still persisted in one or more joints. In most of these cases the substitution of Metacortandracin brought striking improvement which was estimated at 90 to 95 per cent. as compared with 70 to 85 per cent. improvement in response to hydrocortisone. In many of these patients the erythrocyte sedimentation rate became normal for the first time. The daily maintenance dose of Metacortandracin was 5 to 25 mg. In the remaining six patients, who were still suffering much pain despite maintenance doses of hydrocortisone, the change to 30 to 35 mg. Metacortandracin daily raised the estimated degree of improvement from 30 to 50 per cent. to one of 70 to 80 per cent. Minor signs of intolerance to hydrocortisone previously observed occurred also in response to Metacortandracin.

(3) Rubens-Duval reports eleven cases of rheumatoid arthritis, in eight of which corticoid therapy had been given for 1 to 3 years. In these eight cases the substitution of Metacortandracin was usually followed by further improvement in response to a dosage roughly one-half that of hydrocortisone or one-quarter that of cortisone. In the remaining three patients, who had had no previous hormone treatment, improvement comparable to the best results achieved with cortisone and hydrocortisone was obtained with an initial dose of 30 mg. Metacortandracin daily, reduced to a maintenance dose of 20 mg. daily.

(4) Lacapère treated 22 cases of rheumatoid arthritis and two of ankylosing spondylitis with Metacortandracin. The results were "very good" in eleven cases given a maintenance dose of 5 to 20 mg. daily, and "good" in ten. In three cases the treatment was a failure. Signs of intolerance were noted in some patients, these including signs of cardiac failure, "moon-face", gastric pain, cramp, and mental excitement.

The authors' general conclusions are that Metacortandracin has proved twice as active as oral hydrocortisone, and three times as active as cortisone. The initial dose ranged from 30 to 40 mg. daily for 5 to 10 days, after which it was progressively reduced to a maintenance dose which has varied from 15 to 25 mg. daily. The drug was in general well tolerated, but some signs of intolerance have been observed. Kenneth Stone.


At the Centre for Rheumatology, Turin, the authors have treated 38 patients with Metacortandracin for periods varying from 15 to 60 days, the initial suppressive dose being 30 to 40 mg. daily, followed by a maintenance dose of 10 to 15 mg. daily.

In 22 cases of rheumatoid arthritis a typical cortisonelike effect was constantly obtained. The activity of Metacortandracin appeared to be about five times that
of cortisone. Interruption of treatment was followed by relapse in every case, but aggravation of the initial symptoms was never seen, and when treatment was resumed it was found to be as effective as before in the same dosage. Five patients with rheumatic fever also responded well to the new steroid. Other conditions treated with success were acute peri-arthritis of the shoulder, chronic gout, bilateral arthritis of the hip associated with psoriasis, painful Heberden’s nodes, and hypertrophic pulmonary osteo-arthritis.

Minor side-effects were observed when the higher suppressive doses were given but these disappeared on reduction to the lower maintenance doses.

Kenneth Stone.


The authors report the results of the administration at the Ospedale Maggiore, Turin, of Metacortandracin (\Delta 1:4-pregnadiene-17\alpha-21-diol-3:11:20-trione, “delta-cortene”, prednisone) to 32 patients with various forms of acute and chronic rheumatism, among whom were 22 cases of rheumatoid arthritis of various degrees of severity. The dosage ranged from 15 to 50 mg. a day given by mouth in four equal doses. Analysis of the short-term results leads them to assess the antirheumatic activity of the drug as five times that of cortisone, while the side-effects were much rarer and less severe. Details of all cases are presented in a table and a number of graphs illustrate the clinical course in representative cases.

L. Michaelis.


At the Hospital of St. Barnabas, Newark, and the Orange Hospital Center, Orange, New Jersey, the synthetic steroid “Meticorten” (Metacortandracin) was given to 57 patients (including 44 between the ages of 31 and 64) with rheumatoid arthritis which had proved intractable to administration of cortisone and to other treatment. The usual dosage was 20 to 30 mg. daily. In eighteen cases there was complete remission with a normal erythrocyte sedimentation rate (E.S.R.) and no signs of joint inflammation apart from irreversible deformities, while in twenty there was major improvement with minimal residual signs. This treatment was a failure in only one case. A rapid improvement in general well-being was noted; pain and stiffness were relieved in 1 to 7 days, swelling and tenderness were reduced in 1 to 4 weeks, and the E.S.R. returned to normal in 2 weeks. The fibroelastic cellular infiltration was absorbed more completely than during any other similar treatment. Maintenance doses seemed to be more effective than safe doses of cortisone, but it was too early to decide whether “Meticorten fastness” would develop. Pain was relieved in three cases of ankylosing spondylitis and in four of osteo-arthritis of the knees and spine; there was also some relief in three cases of gouty arthritis. Side-reactions which were less prolonged and severe than with cortisone, included insomnia and nervousness, digestive disturbances, palpitation, dyspnoea, precordial oppression, weakness, facial rounding, sweating, hirsutism, and depression. The blood pressure did not change, body weight did not increase, and there was no impairment of water balance.

The authors conclude that Meticorten is four times as potent and one-quarter as toxic as cortisone.

J. N. Agate.


The authors report from the University of Pittsburgh the results in twenty selected cases of rheumatoid arthritis which were treated with prednisone (Metacortandracin) for periods varying from 2 weeks to 3 months. The series included early and late cases of the disease, and fourteen of them had been receiving cortisone or hydrocortisone immediately before the treatment with prednisone was begun. In the majority the maintenance dose of the drug, which was given orally, ranged between 15 and 25 mg. daily, the initial dose being between 20 and 60 mg. daily in four equal doses.

In all the patients there was an increase in functional capacity, as well as objective improvement; of sixteen cases in which the erythrocyte sedimentation rate was raised before therapy, the rate returned to normal in fourteen. The only serious side-effect was dyspepsia; there was no evidence of water retention. The authors were greatly impressed by the results achieved with prednisone in every case, though they emphasize that the period of observation was short. In an addendum to the paper they draw attention to the reported diabetogenic properties of prednisone and suggests that in future studies “this aspect of metabolism will require close scrutiny”.

K. C. Robinson.


Writing from the National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland, the authors describe in detail three cases of duodenal ulcer which occurred in a series of eighteen consecutive cases of rheumatoid arthritis treated with prednisolone or prednisone (Metacortandracin). Routine barium-meal examinations were carried out on all the patients, and in the three cases described an asymptomatic duodenal ulcer was observed to develop within a few weeks of starting the steroid therapy. In two of the cases, treatment with steroid was continued intermittently and the ulcer was seen to heal within a month with ordinary dietary and medical treatment. In the third case, in a Negro woman aged 32, the steroid was withdrawn because of the
development of a severe psychotic depression; it is noted, however, that the patient was already under psychiatric observation because of mild depression when steroid treatment was begun.

The authors emphasize the fact that the ulcers in these cases were asymptomatic and suggest the advisability of the routine administration of an aluminium hydroxide gel to patients receiving prednisone or prednisolone.

K. C. Robinson.


At the Town and County Hospital, Roskilde, Denmark, twelve patients suffering from rheumatoid arthritis were given intravenous injections of 0.1 mg. of “Erasol” (nitrogen mustard) per kg. body weight daily for 4 consecutive days (6 in one case). The condition of all the patients improved during treatment, though in most cases only slightly. The improvement was not maintained for more than a few weeks, however, and most patients suffered from sickness and vomiting, beginning a few hours after administration of the drug. The authors conclude that nitrogen mustard cannot be recommended for the treatment of rheumatoid arthritis except to give temporary relief in cases where other remedies have been tried and failed. Oswald Savage.


Hexamethonium chloride was given for periods of 2 to 9 months to nine patients with active rheumatoid arthritis, three with osteo-arthritis and active rheumatoid arthritis, three with ankylosing spondylitis, and two with “pure” osteo-arthritis. The dosage of hexamethonium chloride, which was 125 mg. on the first day, was gradually increased until side-effects were produced or maximum benefit was obtained, the optimum dose usually being 375 to 500 mg. four times a day. Side-effects were observed in eleven cases. Treatment was not continuous in the patients with rheumatoid arthritis, and they were therefore observed during the withdrawal period and again during a further course of hexamethonium.

There was no evidence of any beneficial response to treatment in the patients with ankylosing spondylitis and pure osteo-arthritis, but in eight of the nine patients with rheumatoid arthritis symptomatic and functional improvement was obtained, although the general activity of the disease was unaffected. The association between rheumatoid arthritis and reflex sympathetic dystrophy is discussed and a theoretical explanation of the mode of action of hexamethonium chloride in rheumatoid arthritis is offered. Kathleen M. Lawther.


In this paper from the Royal Free Hospital, London, three cases are reported in which death from pneumonia occurred during ACTH and cortisone therapy for rheumatoid arthritis.

In the first case, that of a woman aged 64 years who was admitted to hospital in a semi-comatose condition, there was no history of respiratory symptoms and examination revealed neither bronchial breathing nor adventitious sounds. Hypokalaemia was noted on admission. Death occurred on the fifteenth day despite treatment with penicillin, potassium chloride, and ACTH. Necropsy revealed generalized oedema of the lungs and lipid infiltration of the zona fasciculata of the adrenal glands.

In the second case, that of a woman aged 61 years, there was sudden onset of cough, haemoptysis, and dyspnoea. Crepitations but no bronchial breath sounds were audible, although widespread consolidation was found at necropsy 5 days later. There was an associated monocytic leukaemia.

The third patient, a man aged 53 years, had abdominal pain and signs of consolidation at the right base on admission. He underwent laparotomy for suspected perforation because of a previous history of dyspepsia, but no perforation was found; he died 24 hours after the onset of symptoms. Necropsy revealed consolidation at the right base, degeneration of the adrenal glands with haemorrhage into one of them, and two small subacute peptic ulcers.

The authors consider that steroid therapy masked the infections, and recommend that when patients receiving ACTH or cortisone develop pneumonia the dosages of the hormones and of antibiotics should be increased.

I. Ansell.


For a study of the early joint changes in rheumatoid arthritis biopsy specimens were taken from the synovial membrane of the knee from 7 days to 9 months after the onset of clinical involvement of the joint. The clinical and histological features of the eight cases studied are described in detail. Pannus was present in only three cases. The lesions, which varied widely, are discussed under three headings:

1. generalized proliferative inflammation with intimal hyperplasia and inflammatory cell infiltration, chiefly lymphocytes with a focal distribution;
2. fibrin-like deposits and necrobiosis;
3. vascular lesions, such as hyperplastic thickening of vessel walls and focal juxtavascular round-cell infiltration.

Active vasculitis was found only in the biopsy specimen taken 7 days after the onset of joint involvement. The authors state that on the whole the lesions differed from those characteristically found in the fixed joints of the later stages of rheumatoid arthritis. In the earliest stages the reaction was confined almost entirely to the intima. Lymphocytic nodules and villous hypertrophy
were seen in specimens taken more than 4 months after the onset. Some perivascular haemorrhage was also observed. [The account of this investigation repays detailed study.]

E. G. L. Bywaters.


After briefly reviewing the incidence of and morbidity from the rheumatic diseases in the United States, the author describes an attempt made at the Goldwater Memorial Hospital, New York, to reduce disability by combining rehabilitation with medical treatment during the active phase of the disease process instead of waiting for activity to subside before starting rehabilitation. In a group of 38 patients with chronic rheumatoid arthritis, eighteen of whom were severely crippled and twenty less severely disabled, rehabilitation measures were started as soon as the maintenance dosage of cortisone or hydrocortisone had been established, the period of observation in hospital being 7 to 21 months.

Of the eighteen severely crippled patients, seven were totally self-sufficient and seven partially so when discharged; four remained in hospital. All the patients who were less severely disabled were discharged, fifteen being totally self-sufficient and five partially so. One patient in the former group and seven in the latter were able to take up full-time employment.

Kathleen M. Lawther.


Experience of the first year's working of a household training unit for disabled women at the Devonshire Royal Hospital, Buxton, is described. The unit consists of two small rooms, the larger being a twin kitchen, with two separate sinks connected respectively by a ramp to a gas and an electric cooker, and the other a "utility room" for laundry and other household tasks. About 150 in-patients used the unit during the year, and the results obtained in 81, the majority of whom (59) had severe rheumatoid arthritis, are analysed. Before retraining, 23 of these patients were completely incapable of doing any housework, and a further 44 were capable of only light work; after retraining in household duties, kitchen methods, and work simplification, none of the 81 patients remained completely incapable, and 52 could run a normal household.

The authors comment that such a unit is cheap to instal and to run, and that since housewifery is the largest "industry" in any country, retraining of the housewife is a rewarding process. B. E. W. Mace.


(Osteo-Arthritis)


(Spondylitis)


This paper presents the preliminary findings of an investigation carried out by the authors at the Postgraduate Medical School of London under the auspices of the Medical Research Council's working party for research on leukaemia, and is based on information concerning 9,364 cases of ankylosing spondylitis treated with x rays at 37 radiotherapy centres in the United Kingdom. Out of 4,297 patients whose sex was recorded, 3,679 were male and 618 female, a ratio of 5·95 to 1. The age of the patients when first seen at a radiotherapy centre was noted in 2,697 cases; an age-distribution table shows that 92 per cent. of these were between the ages of 15 and 54. Information obtained from seventeen centres showed that of 3,085 patients, 1,731 (56 per cent.) were returning periodically for examination or were known to have died, while of 2,361 patients, 797 (33·8 per cent.) had more than one course of treatment.

So far, records have been obtained of 25 patients who have developed leukaemia, but this figure is likely to be incomplete as only about 44 per cent. of the 9,364
patients have been kept under observation; of these 25 patients, 21 have been certified as dying from leukaemia. In four cases ankylosing spondylitis and leukaemia were considered to co-exist when irradiation was first begun. The authors have calculated from the Registrar-General's returns for death-rates for leukaemia for the period 1940-53 that among 9,364 individuals of the same age distribution the expected number of deaths from leukaemia would be less than four. If every case in the present series were included, the ratio of observed deaths to expected deaths from leukaemia would be 5·4 to 1, while if only those cases satisfactorily followed up are included this ratio rises to 9·5 to 1.

The reported spontaneous co-existence of ankylosing spondylitis and leukaemia suggests that patients with spondylitis may have an increased susceptibility to leukaemia. This possibility is fully discussed and accepted by the authors, but after reviewing both their own evidence and that in the available literature, they come to the conclusion that x-irradiation plays a real part in the genesis of leukaemia. They emphasize, however, that in many cases of spondylitis radiotherapy is the only therapeutic measure which may successfully terminate a disease often characterized by great suffering and sometimes by early death. This form of treatment is therefore not necessarily contraindicated in cases of ankylosing spondylitis, provided that the diagnosis is definitely established. They suggest that repeated courses of irradiation should not be given unless absolutely necessary, as re-treatment appears to increase the likelihood of the development of leukaemia.

A. M. Jelliffe.


A study of 150 cases of the Fiessinger-Leroy-Reiter syndrome leads the author to state that this syndrome assumes one of the aspects of a fairly typical rheumatic disease. It is epidemiologically similar to infectious and parasitic colitis. The clinical manifestations are polymorphous. Some infection is often to be found as an initial factor. Hormonal treatment appears to be more effective than antibiotics against the rheumatic process.

S. Vallon.

C-reactive Protein Test in Ankylosing Spondylitis and in Other Rheumatic Diseases. (Il "test" della proteina C nella spondilite anchilosante ed in altre malattie reumatiche.) Luccherini, T., Conestabile, E., and Natali, P. (1955). Reumatismo, 7, 214. 3 figs, 14 refs.

In this paper from the Rheumatological Centre of the University of Rome the authors report an investigation into the value of testing for the presence of C-reactive protein in the serum of patients affected by ankylosing spondylitis and other rheumatic diseases. The technique used for the test was that of Hill (Lancet, 1952, 2, 558; Abstracts of World Medicine, 1953, 13, 239), in which the patient's serum reacts in vitro with a solution of pneumococcal C-polysaccharide.

A total of 38 cases were examined, consisting of nineteen cases of ankylosing spondylitis, four of rheumatic fever, fourteen of rheumatoid arthritis, and one of disseminated lupus erythematosus. In rheumatic fever C-reactive protein was constantly present, whereas in rheumatoid arthritis it was present only in the acute phase. In only five of the cases of ankylosing spondylitis was a positive reaction obtained, these patients being in the initial phase of the disease, when the activity of the process was indicated by severe clinical manifestations and by a high erythrocyte sedimentation rate. (The reaction was positive in the single case of disseminated lupus erythematosus studied, but this may have been due to super-added pyogenic infection.) Treatment with phenylbutazone had no effect on a positive reaction for C-reactive protein, whereas on substituting treatment with hydrocortisone the reaction rapidly became negative in many cases.

The author's conclusion is that the test for C-reactive protein is of some value in determining whether the rheumatic process is in an active or a quiescent state.

E. Forrai.


In the view of the author of this paper from the University of Maryland, Baltimore, the term "spondylitis of the cervical spine" is not sufficiently descriptive and the term "spondylochondrosis" is preferable, since it takes into account both the cartilaginous protrusion and the osteophytic overgrowth of the vertebrae. In a review of the literature he points out that rupture of the intervertebral disk has been recognized as a clinical entity since the classic description of Mixter and Barr in 1934. He then describes ten cases of cervical spondylochondrosis, in seven of which the long tracts were primarily involved, with resulting paraplegia, in two the anterior roots only, producing the "anterior root syndrome", and in one both the long tracts and the anterior roots were markedly involved. The clinical and radiological findings and the treatment are described.

The author then discusses [with excellent diagrams] the anatomy of the spinal canal in the cervical region in 100 cases. The antero-posterior width of the spinal canal of the fifth vertebra was measured, and the average, both in the group as a whole and in those with normal vertebrae, was found to be 1.3 cm., the narrowest being 1 cm. and the widest 1.8 cm. It is suggested that the size of the cervical spinal canal is a significant accessory factor in the causation of symptoms in spondylochondrosis.

Discussing treatment of the condition the author states that conservative measures are of little or no value unless the lesions are minimal and non-progressive. Minimal symptoms may be present for many years and may then be followed by a fairly sudden exacerbation and marked progression; when this occurs surgical treatment should be given without delay. Laminectomy with section of
the dentate ligaments is the treatment of choice; removal of the protruding ridge of bone from the arthritic process is a hazardous procedure. Foramenotomy is indicated where the intervertebral foramen shows that it is tight around the root. The results of operation in the author’s series were excellent in four cases, moderate in three, and slight in one. There was no improvement in one case and in one the condition was worse.

[This is a good paper. The author has taken a great deal of trouble, particularly in the anatomical study of the cervical spine.] Leon Gillis.


(Miscellaneous)


Phenylbutazone is an analgesic which has been used for the treatment of rheumatism and conditions such as osteo-arthritis. Its use, however, is sometimes accompanied by toxic side-effects, the most serious being haemorrhage from the gastro-intestinal tract. The present authors record in detail the case of a woman of 29 who had had rheumatoid arthritis as a child and occasional transitory arthritis subsequently. She had recently consulted her doctor because of a more persistent pain in the lumbar region, for which she was given phenylbutazone, a total dose of 2-9 g. being taken over a period of 5 days (250 mg. on the first day, 850 mg. on the second day, and 600 mg. for each of the 3 following days). On the second day of treatment she experienced burning epigastric pain and her stools were black. On stopping treatment the epigastric pain disappeared, but 6 days later she had a severe haematemesis and for the next 12 days her condition remained serious in spite of blood transfusions and other treatment. Radiological examination of the stomach did not establish the presence of an ulcer with any certainty. The patient eventually made a good recovery. _R. Wien._


The author reports the results obtained with phenylbutazone in the treatment of 161 cases of rheumatoid arthritis and von Bechterew’s disease at the Rheumatism Clinic, Rotterdam. Pain was relieved in a considerable number of cases. The toxic side-effects, which were encountered in 27 per cent. of the patients (who received a dosage of 600 mg. per day later reduced to 400 or 200 mg. daily 5 days per week) were probably less frequent and less severe than with “pyramidon” (aminopyrine), but objective improvement was very seldom observed.

R. Crawford.


The clinical features of an illustrative case are described, and the aetiology, differential diagnosis, and treatment are discussed.

Three cardinal points stand out in the diagnosis:

1. The abrupt onset of urethritis, arthritis, and conjunctivitis;
2. The repeatedly negative smears and cultures for gonococci and other pathogenic organisms; and
3. The usually self-limiting course.

Treatment, in the absence of any definite aetiology, is empirical, and includes antibiotics, ACTH, and cortisone. _J. R. Hudson._


Description of the ocular symptoms of osteitis deformans—optic atrophy, papilloedema, and exophthalmos are frequent, while sclerotic macular affections, retinal haemorrhages, corneal degeneration, or cataract are less frequently found. The relationship of angiod streaks or the full Groenblad-Strandberg syndrome (angiod streaks and pseudoxanthoma elasticum) to osteitis deformans is also discussed. _W. Leyhecker._


ANNALS OF THE RHEUMATIC DISEASES


Disk Syndrome


Gout


There are apparently several hundred methods of determining the uric acid level in the blood, but none is entirely satisfactory. In this paper from the Hôpital Rothschild, Paris, the authors describe their own method which, if not more accurate than the others, at least has the merit of simplicity. In this the uric acid is determined by a modification of the method of Folin and Denis, first on the plasma, and then on heparinized whole blood, the object of heparinization being to prevent retraction of the erythrocytes. From these two results together with the haematocrit value the uric acid content of the erythrocyte can readily be calculated.

Using this method the authors showed that the uric acid level in the erythrocytes in a group of patients during attacks of acute gout was "remarkably high", but was not always accompanied by a rise in the plasma uric acid level. The reduction in uric acid level following administration of phenylbutazone to these patients was much more marked in the erythrocytes than in the plasma; also, in the course of the treatment the pain of acute gout often subsided simultaneously with the fall of the uric acid level in the erythrocytes.

In a group of non-gouty subjects also it was found that a high level of uric acid in the erythrocytes was often accompanied by a normal level in the plasma; some of these patients had some other form of arthralgia, while others had some metabolic disorder or migraine.

Joseph Parness.


Pararheumatic (Collagen) Diseases


In this paper from the University of Minnesota Hospitals, Minneapolis, the author describes the occurrence of circulating anticoagulants in three patients with
systemic collagen disease. There was evidence that two of the patients were suffering from disseminated lupus erythematosus, while the third was under observation for a drug reaction following antibiotic therapy. Circulating anticoagulants usually give rise to a haemorrhagic state with clinical features similar to haemophilia; in the present cases, however, the clinical manifestation of abnormal haemorrhage was slight in comparison with the laboratory evidence of interference with the coagulation mechanism. In one case there was transplacental passage of the anticoagulant, the latter persisting in the patient's newborn infant for 7 weeks.

The important laboratory features were similar in all three cases, and consisted in prolongation of the whole-blood clotting time and recalcification time, and defective prothrombin consumption. It was shown that the addition of a small proportion of the patients' plasma to normal plasma caused a significant lengthening of the recalcification time in the latter. Similarly the addition of the patients' plasma to normal blood caused the prothrombin consumption of the latter to become defective. These findings proved the presence of a circulating anticoagulant. Determination of one-stage clotting time showed that this too was prolonged, and in a mixture consisting of normal and patient's plasma the same phenomenon was observed.

The author concludes that the anticoagulant present in these cases acted as an antithromboplasin, and that its occurrence in association with other manifestations of hypersensitivity and the fact of its transplacental transfer suggest that the mechanism of development was immunological. A subsidiary study showed that circulating anticoagulants were present in three out of a series of thirty patients with disseminated lupus erythematosus and allied conditions, an incidence of 10 per cent. The authors have little comment to make on treatment, but suggest that prolonged administration of cortisone might have some effect, since "the effect of this drug on other types of immune antibodies like haemagglutinins has been well established".

"Focal necrosis" involved part of the glomerular tuft in seven cases. These areas showed a background of hyaline substance with superimposed bodies of haematoxyphil material. The latter were about the size of an erythrocyte and stained purple with haematoxylin and eosin, in contrast to pyknotic nuclei, which stained blue. Capillary-loop thickening, seen in ten cases, was due to coating of the capillaries with hyaline substance smudged with haematoxyphil material. Proliferative glomerulitis was observed in eight cases and arteriolar hyaline necrosis in two only. In cases in which glomerular changes were severe there were interstitial oedema, interstitial cellular proliferation without marked fibrosis, and tubular atrophy and regeneration. In five cases there were tubular casts which gave a similar reaction to staining as the hyaline material.

As regards the histological differentiation of D.L.E. from subacute bacterial endocarditis the areas of focal necrosis in the latter do not contain haematoxyphil bodies and the eosinophil material present is fibrin, which lacks the sharp, refractile outline of the hyaline substance of D.L.E.

Capillary-loop thickening is sometimes seen in acute nephritis, eclampsia, and scleroderma, but shows no haematoxyphil smudging. Thickening due to amyloid is superficially similar, but it also involves the vasa recta (unlike D.L.E.) and may be differentiated by specific stains.

Although Klemperer's hypothesis that the source of the haematoxyphil material and hyaline substance is degraded nucleoprotein is not proven, it is, in the author's view, the only convincing explanation at present.

M. C. Berenbaum.


Of 26 patients aged 25 to 73 suffering from chronic lupus erythematosus who were treated with synthetic antimalarials, 24 were given "Atebrin" (mepacrine) and two "Resoquin" (chloroquine) in initial doses of 200 to 500 mg. daily. Apart from two patients who are still under treatment, the other 24 were followed up for periods between one and 12 months (average 6). Re-examination showed that the lesions had completely healed and remained so in ten cases, four patients were greatly improved, four improved, two slightly improved, and three unchanged; in the remaining three patients the condition recurred at 2, 2, and 6 months respectively. A complication of treatment in the form of an exfoliative dermatitis occurred in one case, while three other patients suffered from nausea and vomiting.

Eric Dunlop.


A large number of cases of systemic lupus erythematosus have recently been studied at the Johns Hopkins
Hospital, Baltimore, and from these cases 100 were selected for analysis of the radiological findings. The diagnosis was established by typical clinical findings in 22 cases and histological evidence in the others.

Pleural thickening, usually present at the base of both lungs, was the most frequent abnormality, occurring in 81 cases. Massive effusion was rare. In 52 cases there were lesions in the lung parenchyma, which usually appeared as ill-defined areas of infiltration, although linear plaques were also seen in many cases. Cardiac enlargement, which was present in 53 cases, was due to pericardial effusion in only three; in the remainder it was thought to result principally from myocarditis. Although joint involvement is a prominent clinical feature of systemic lupus erythematosus the radiographs usually showed only a minimum degree of osteoporosis. Splenic enlargement, which is another clinical feature, was detected radiologically in only 34 patients.

There were a number of other incidental findings, such as impaired renal function on excretion pyelography and lung abscess due to secondary infection. The authors conclude that serial chest radiographs will demonstrate the characteristic features in most cases; they point out that even splenic enlargement was more often detected on well-exposed radiographs of the chest than on radiographs of the abdomen.

D. E. Fletcher.


After a review of the literature, the author of this paper from the University of Genoa critically examines the value of the L.E.-cell test in cases of systemic lupus erythematosus without skin eruptions. He describes five such cases in which the reaction to the L.E.-cell test was positive. In the examination of these cases he found that the number of L.E. cells and rosettes increased with the severity of the disease, and that the results of tests performed with defibrinated blood were more frequently positive than those of tests with blood containing anticoagulants. Whereas with the anticoagulant technique there were no false positive reactions, with the defibrination method the clumping of neutrophil granulocytes could sometimes be confused with rosettes, and tar cells were seen which closely resembled L.E. cells. The author has observed L.E. inclusion bodies in eosinophil granulocytes. He questions whether the L.E.-cell phenomenon should be considered pathognomonic in view of the positive results occasionally obtained in patients with drug allergy.

E. G. Rees.


A method for the quantitative assay in vitro of the effect of mepacrine ("Quinacrine") on the L.E.-cell phenomenon is described in this paper from the University of Southern California and the County Hospital, Los Angeles. Standard solutions of the drug were mixed with potent L.E. plasma and after an interval a 20 per cent. suspension of leucocytes and some indicator of phagocytic activity, such as a solution of indian ink or a suspension of coagulase-positive staphylococci, was added. Half an hour later the mixture was examined for L.E. cells. It was found that the drug completely inhibited the L.E.-cell phenomenon at concentrations between 0.2 and 0.4 mg. per ml., depending on the potency of the original plasma. It was not leukotoxic in concentrations of less than 0.8 mg. per ml.

The author states that the highest plasma level of mepacrine that can be attained in patients taking the maximum tolerated dose is 0.1 mg. per 100 ml. However, the concentration of mepacrine in the leucocytes is 100 to 300 times the plasma level, and is well within the inhibitory range. In four patients given large doses of mepacrine the L.E.-cell phenomenon disappeared within 2 weeks; with cortisone alone 4 to 6 weeks was required to achieve the same result. It is concluded that the technique described may prove to be a valuable screening method for useful agents in the treatment of systemic lupus erythematosus.

E. G. Rees.


In 1948 an investigation was begun at Johns Hopkins University and Hospital, Baltimore, the aims of which were:

(1) to investigate the validity of the treponemal immobilization (T.P.I.) test, and
(2) to study the phenomenon of "biologic false positivity".

In this paper the authors are mainly concerned with the second point, but they briefly quote the work of Zellmann, who concluded that a valid negative T.P.I. test differentiates between a syphilitic infection and a biological false positive (B.F.P.) reaction with a margin of error of about 2 per cent., provided treated early syphilis and definite clinical evidence of syphilis are excluded.

B.F.P. reactions may be "acute" or "chronic"; the acute reaction occurs shortly after an acute infectious illness, and usually disappears within 6 months. The aetiology of the chronic reaction was in 1948 almost completely unknown, but in the intervening 6 years the authors have studied 148 chronic B.F.P. reactors, of whom 104 (70 per cent.) were female. When first seen only four patients were suffering from overt disease which might have been related to the phenomenon, while of the remainder, two-thirds had no symptoms at all, and one-third had only minor symptoms which were not obviously relevant. In all cases the standard serological tests for syphilis had been positive for at least one year.

However, during the period of observation, ten patients developed definite systemic lupus erythematosus, seven developed rheumatoid arthritis (which may be the first manifestation of systemic lupus erythematosus), and 45 were tentatively diagnosed as possible or probable cases of lupus erythematosus on clinical grounds, though without pathological confirmation. The most common...
clinical features of systemic lupus erythematosus, as seen in this series, are tabulated, short clinical histories of representative patients are given, and the positive laboratory findings are briefly described. Mild anaemia was fairly common in the female patients, but leucopenia was unusual. Chemical and electrophoretic tests on the serum proteins showed some abnormality of the globulin fraction in 90 per cent. of the cases. In over half the cases the erythrocyte sedimentation rate was persistently raised. It is also noted that the reaction was first observed when half the female patients and one-quarter of the males were under the age of 25. It is suggested that the finding of a B.F.P. reaction should be an indication for a search for the cause.

The clinical course of systemic lupus erythematosus developing under these circumstances appears to be exceedingly chronic, compared with the usual picture of the disease. It is hoped that continuation of this study over a further period of years will give a more accurate picture of the natural history of this disease than can be obtained from the retrospective study of advanced cases.

Nigel Compston.


The close relationship between dermatomyositis and scleroderma has been recognized for some years. In scleroderma associated visceral lesions are so common that the term “progressive diffuse sclerosis” has been suggested. The present authors, writing from the Central Middlesex Hospital, London, consider that the clinical and histological features of dermatomyositis, progressive diffuse sclerosis, and disseminated lupus erythematosus, may overlap sufficiently to render differential diagnosis impossible in some cases, and they therefore suggest an even more general term—namely “viscero-cutaneous Collagenosis”.

Seven cases are described in detail and excellent photomicrographs are reproduced. One patient in whom dermatomyositis was diagnosed died 11 years later from a condition in which the lesions resembled those of progressive diffuse sclerosis; it would seem that these two conditions are stages in the same disease. At necropsy on two cases clinically resembling dermatomyositis there were histological skin changes of scleroderma. In another case of scleroderma of 20 years’ duration some histological changes of dermatomyositis and disseminated lupus erythematosus were found. The clinical diagnosis of polyarteritis nodosa in another case was not substantiated at necropsy, the features observed being common to disseminated lupus erythematosus, dermatomyositis, and progressive diffuse sclerosis.

The authors state that the changes in the nail fold clinically regarded as characteristic of disseminated lupus erythematosus and dermatomyositis consist in patchy extravascular fibrinoid necrosis associated with capillary thromboses—an unusual combination of collagen disease and acroancrosis. Focal necrosis and focal fibrosis respectively in the adrenal glands in two cases of dermatomyositis were considered to be early and late stages of the same process.

[For the detailed description of the histological findings in these cases the original paper should be consulted.]

Nigel Compston.


The gross and histological lesions in the lungs of 54 patients dying from disseminated lupus erythematosus are described in this paper from the Mayo Clinic. Secondary infection and evidence of vascular damage were found in most of the cases. No actual lesions such as “fibrinoid degeneration” were observed in the vessel walls, but in nine cases there was a curious mucinous oedema in the perivascular and peribronchial tissues with some spread into the alveolar walls. It is suggested that this may be the precursor of fibrinoid change.

A. C. Lendrum.


The authors describe seven cases seen at the Hospice de la Salpêtrière, Paris, in which a neuritic disorder developed in the course of periarteritis nodosa. Of these, three conformed to an asymmetrical multineuritis, three showed a symmetrical polynervitic distribution, while in the seventh case the early neurological picture was soon overshadowed by the muscular, articular, and cutaneous manifestations of the disease. Pathological confirmation was obtained by biopsy or (in three cases) at necropsy. In three of the cases the administration of ACTH or cortisone in doses of 100 mg. per day appeared to produce beneficial results, although one of the fatal cases was also treated with corticoids. (The reproduction of a photomicrograph of material obtained at one of the necropsies shows an excellent specimen of an obliterated arteriole in a spinal root.)

The special clinical features in these cases to which attention is drawn included pyrexia and constitutional disorder, loss of weight, anaemia, the presence of eosinophilia with a moderate polymorphonuclearcytosis, and a constant elevation of the erythrocyte sedimentation rate; urinary disorders, with casts, albuminuria, and microscopiacal haematuria, were present in most of the cases, and in one porphyria occurred. Abdominal pain was prominent in four cases, and oedema also in four. The occurrence of other neurological manifestations (apart from the polyneuritis or mononeuritis multiplex) such as mental confusion (one case), fits (two cases), and coma (one case), indicate the pleomorphism of the condition. The importance of muscle biopsy for diagnostic confirmation is stressed, although it is pointed out that a negative biopsy result does not exclude absolutely the possibility of periarteritis.

L. A. Liversedge.

In this paper from St. Mary's Hospital, London, the author first points out that from experiments in animals and clinical observations it would appear that polyarteritis nodosa is a manifestation of anaphylactic hypersensitivity to various antigens. Pathologically, necrotizing, inflammatory, obliterative lesions of the small arteries are widespread throughout the body. Males are more commonly affected than females and the age incidence is usually 30 to 40 years. Fever is generally present either at the onset or later in the disease. The prognosis is poor, but some patients have benefited from administration of ACTH or cortisone, although the long-term results of this form of treatment have yet to be assessed.

Radiologically, the changes seen in the lung fields—apart from terminal manifestations of heart failure, such as gross cardiac enlargement and pulmonary oedema—take the form of infiltrations of very varying pattern and sometimes of pleurisy with effusion. Six cases are briefly reported and radiographs are reproduced. The lesions tend to be transient and migratory and there may be complete clearing of the lung fields between attacks. Post-mortem examination revealed multiple granulomata and areas of necrosis in the small vessels at different stages of development. The author discusses the radiological changes in relation to eosinophilia, which was a feature in three of the cases described; he considers that some of these may be of the same nature as "eosinophilic lung", but that multiple granulomata and, to a lesser extent, infarcts and small atelectases also play a part in creating the bizarre picture. A. M. Rackow.


General Pathology

Antimyocardial Antibodies in Rheumatic Fever. [In English.] Rejholec, V., and Wagner, V. (1955). Experientia (Basel), 11, 278. 1 fig., 6 refs.

A brief report on the quantitative estimation of auto-antibodies in the serum of patients suffering with rheumatic fever, rheumatoid arthritis, and glomerulonephritis is presented from the Research Institute of Rheumatic Diseases, Prague, and Charles University, Pilsen. Organ antigens were prepared from normal human kidney, myocardium, and liver by extraction with 1:1 per cent. sodium chloride solution and the extracts used to treat collodion particles by Cavelti's method. The "sensibilized" particles were then incubated for one hour at room temperature admixed with geometric dilutions of the patient's serum and the presence of agglutination determined with an agglutinoscope. Antimyocardial antibodies were found in the serum at an average titre of 1 in 20 in six out of eight cases of rheumatic fever; at an average titre of 1 in 16 in eight out of ten cases of "acute tonsillitis showing the so-called myocardial E.C.G. curve"; and at a titre of 1 in 4 in all of three cases of rheumatoid arthritis. These antibodies were present at a low titre in the serum in most of sixteen cases of active glomerulonephritis, but in none of ten cases of latent glomerulonephritis. In a control group of 57 healthy subjects these antibodies were present at a low titre in a small number of cases. It was found that in cases of acute rheumatism the titre of antimycocardial antibodies were reduced as a result of salicylate therapy.

Harry Coke.


At the Hektoen Institute for Medical Research (Cook County Hospital), Chicago, the authors investigated the value of two antigen—antibody reactions as a means of determining rheumatic fever activity; the trial was carried out on 78 patients with rheumatic fever (active and inactive) and 77 controls.

In Method I the serum of rheumatic fever patients was used as the antibody and sheep erythrocytes coated with heat-killed Group-A β-haemolytic streptococci from rheumatic fever patients as the antigen, complement being then added to produce haemolysis.

In Method II Group-A β-haemolytic streptococcus antiserum from immunized rabbits was employed as antibody and the patient's erythrocytes as antigen.

Method I, using the patient's serum as the antigen source, was found to be the more sensitive and showed better correlation with the clinical state. Of the patients in whom the disease was clinically active, 98 per cent. gave a positive haemolytic reaction, as against 89 per cent. with the agglutination method. In those in whom the disease was considered inactive, the respective positive reactions were 48 and 30 per cent. The height of the titre did not indicate the severity of the process, and showed no correlation with the erythrocyte sedimentation rate. Treatment with cortisone or salicylates did not interfere with the determinations. In all the 77 control subjects the reactions were negative by both methods. It is concluded that these reactions are of practical value in assessing the activity of rheumatic fever, as well as in its diagnosis.

G. W. Csonka.


The high percentage of glycine in the molecules of collagen and elastin compared with those of the other body proteins suggested to the authors that in rheu-
matoid arthritis and other diseases characterized by lesions affecting the connective tissues glycose metabolism might show some detectable disturbance. Benzoioc acid being detoxified by conjugation with glycine and excreted as hippurate by the kidney, they studied the effect on the serum glycine and alanine levels and on urinary hippurate excretion of the intravenous administration of 1·77 g. sodium benzoate after a 12-hour fast to 91 non-rheumatic control subjects (some with other diseases of bones or joints), 127 patients with rheumatoid arthritis or anklyosing spondylitis, 24 with rheumatic fever or inactive rheumatic heart disease, and seven with diffuse collagen disease (disseminated lupus erythematosus or scleroderma). Tests of renal and hepatic function were carried out and all patients with gross disorders of these organs were excluded (although 16 per cent. of the patients studied had albuminuria and 20 per cent. had minor defects of hepatic function as shown by the "bromsulphophthalein" excretion test or determination of plasma protein partition).

Comparison of the fall in serum glycine levels following the administration of sodium benzoate in the various groups revealed a considerable overlap between the values obtained for the non-rheumatic and rheumatic cases, while even in the same individual marked variations occurred which did not correlate closely with changes in the clinical condition or the erythrocyte sedimentation rate. Statistically significant differences were demonstrated, however, which "can be interpreted best as indicative of reduced reservoirs of readily available glycine in the rheumatoid state, particularly when clinically active disease is present". No such correlation was found between rheumatoid activity and the changes in the serum alanine level or urinary hippurate excretion.

R. E. Tunbridge.


In 33 cases of rheumatic fever and six cases of rheumatic heart disease without active rheumatism studied at the Jewish Chronic Disease Hospital, Brooklyn, New York, the plasma fibrinogen level was estimated at frequent intervals and compared with the erythrocyte sedimentation rate (E.S.R.). The latter was determined by Wintrobe's method, and the former by the spectrophotometric measurement of the increase in optical density of the plasma during clotting. In addition, tests for the presence of C-reactive protein (C.R.P.) were carried out at least once in every case.

An increase in the plasma fibrinogen level was found only when there was clinical evidence of active rheumatism, and was sustained only in cases with a protracted clinical course. The level remained normal in cases in which an elevated E.S.R. was unaccompanied by other evidence of activity and in cases of inactive rheumatic heart disease complicated by respiratory infection. If the level was increased initially, it fell rapidly when cortisone was given, often becoming abnormally low. In those cases in which cessation of hormone treatment was followed by a "rebound" of clinical activity the plasma fibrinogen level often rose transiently, this rise being preceded by an increase in E.S.R. and re-appearance of C.R.P. In general, the plasma fibrinogen level returned to normal before C.R.P. disappeared and long before the E.S.R. fell to normal, and the authors suggest that such a fall is a reliable indicator of a recession of the inflammatory process rather than of its complete subsidence.

S. C. Milazzo.


At the Clinic for Rheumatic Diseases, Bad Kreuznach, Germany, 498 samples of serum from 302 patients with various forms of rheumatic disease were examined for the content of protein-bound carbohydrate. The results showed that the serum proteins of these patients contain fixed carbohydrates consisting mainly of galactose, mannose, and glucosamine. These components can be isolated from the proteins and quantitatively determined. This procedure revealed that glucosamine levels rise proportionately with the activity of the disease in most cases of acute rheumatoid arthritis and anklyosing spondylitis, but a similar rise was seen only rarely in cases of fibrositis, osteo-arthritis, and quiescent rheumatoid arthritis. Quantitative determination of the glucosamine level was found to be useful in evaluation of the activity in chronic inflammatory rheumatism, and also in the differential diagnosis between inflammatory and degenerative types of rheumatic diseases, being thought to be more useful in this respect than the erythrocyte sedimentation rate.

In discussion the author states that the increase in the serum content of protein-fixed carbohydrates is caused by a rise in the level of carbohydrate-rich globulins and a fall in that of albumins, as well as a rise in the carbohydrate content of some other serum protein fractions. An increase in the total serum proteins was not found to be a factor, nor is it thought that the increase is due to the appearance of abnormal carbohydrate–protein fractions.

G. W. Csonka.


Working in the clinical laboratories of the Hanusch Hospital, Vienna, the first-named author, employing an anti-human-globulin (A.H.G.) deviation technique, has shown that the serum of patients suffering from rheumatoid arthritis and rheumatic endocarditis contains a substance with specific properties against cells of the heart, muscle, and joint capsules. Serum from healthy individuals and from patients suffering from diseases
such as tuberculosis and pneumonia did not contain this substance, while the latter had no effect on cells of the spleen or liver. It was concluded that the substance was of the nature of an incomplete antibody with a specific activity against fibro-muscular tissue. In the further studies here reported its properties were investigated by a deviation technique (using Coombs serum) and by elution. [For details of the procedures the origin should be consulted.]

Samples of serum from thirteen patients with cardiac disease incubated with cardiac tissue and mixed substrate; with eight of these, from patients with active rheumatic endocarditis, definite A.H.G.-deviation was obtained, but four tests against muscle substrate gave no deviation. In one case, which ultimately proved fatal, it was actually found possible to use ante-mortem serum against the patient’s own tissues. In two cases it was shown that the level of circulating antibody decreased with clinical improvement. Of samples of serum from five patients with cardiac disease who acted as controls, four showed no deviation with muscle, heart, and mixed substrate, while the fifth revealed antibody activity against muscle and mixed substrate but not against heart substrate.

The sera of eight rheumatoid arthritic patients were next examined, those of five patients with neurasthenia and neuralgia being tested as controls. The former showed the presence of an antibody with specific action against muscle cells and mixed cells (from muscle, joint-capsules, and heart); four of these sera showed no specificity towards heart cells, but the remaining four revealed some specificity, and inquiry showed that three of these patients had old cardiac damage. The five control cases yielded negative results. Absorption and elution techniques gave comparable results.

David Preiskel.

**Reaction of Streptococcal Agglutination relative to the RAS Factor in Rheumatoid Arthritis. Parts I and II.**


The agglutination by sera from cases of rheumatoid arthritis of living Group-A streptococci pathogenic to man (L agglutination), of killed, autoclaved streptococci of the same origin (O agglutination), and of sensitized sheep erythrocytes was studied at the University of Lund, Sweden. All these tests are known to give positive results in varying degrees in cases of rheumatoid arthritis. Electrophoretic separation of the different serum protein components was first undertaken, and the agglutination titre of the various components estimated. The L and O agglutinins were inconsistently found in the slower moving fractions of gamma globulin, while the R.A.S. factor (the unidentified “rheumatoid arthritis serum” factor responsible for the agglutination of sheep erythrocytes) was recovered from the faster moving gamma- and beta-globulin fractions. The titre of the R.A.S. factor was found to reach its maximum in those fractions in which those of the L and O agglutinins are decreasing or absent, showing that these agglutination factors are not identical.

Sera treated with carbon dioxide at 4° C. showed a significant reduction in titre of the L agglutinins and of the R.A.S. factor, without change in that of the O agglutinins. Titration of the precipitate formed with CO₂ demonstrated the presence in it of part of the R.A.S. factor but no L agglutinins. It is suggested that these experiments show that there is a relationship between L agglutinins and the R.A.S. factor whereas the O agglutination reaction appears to be entirely independent of the other two. Sera were then treated with 0.5 per cent. aluminium silicate (bentonite), which has been shown to precipitate only beta-globulins. This caused the complete disappearance of L agglutinins and the R.A.S. factor without having any effect upon the O agglutinin titre. However, the addition of electrophoretic fractions with a high titre of R.A.S. factor to the bentonite-treated serum resulted in reactivation of the L agglutinating factor without influencing the titre of the O agglutinins. As L agglutinins are associated mainly with the slow-moving gamma globulin and the R.A.S. factor with the fast-moving fraction this was not due to the introduction of fresh L agglutinins, but to a specific relationship between the R.A.S. factor and L agglutination.

Since human pathogenic streptococci contain polysaccharides closely related to certain substances present in mesenchymal tissues, namely, N-acetyl glucosamine and hyaluronic acid, the agglutinins which react with the streptococcal antigens in rheumatoid arthritis might be auto-antibodies developed against mesenchymal tissue products. In an attempt to test this hypothesis sera from cases of rheumatoid arthritis were treated for one hour at 52° C. with streptococcal C-substance, hyaluronic acid, N-acetyl glucosamine, and autoclaved synovial tissue and their agglutination titres then reetermined. L agglutination was found to be completely inhibited by synovial tissue, but not by the other polysaccharides. The effect on O agglutination was more variable, although all the substances tested generally reduced the titre and in some cases inhibited agglutination.

In view of these findings the author puts forward a new concept of the pathogenesis of rheumatoid arthritis, envisaging four phases:

1. Hyaluronidase production is increased as a result of various disturbances, infectious, hormonal, and traumatic.
2. Depolymerization of mesenchymal polysaccharides and hyaluronic acid occurs as a result of this increased enzymatic activity.
3. Depolymerization products become bound to local or serum proteins and become antigenically active, with the production of auto-antibodies.
4. An auto-allergic reaction results, producing inflammation and proliferation of synovial tissue and maintaining the continuous activity that is the normal course of rheumatoid arthritis.

[This is an important and significant addition to knowledge concerning the agglutination phenomena occurring in sera from cases of rheumatoid arthritis and their relationship, and to the development of the concept of rheumatoid arthritis as an auto-allergic reaction.]

Harry Coke.

After the administration of a therapeutic dose of heparin in vivo or the addition of a minute quantity to a blood sample in vitro, the authors have observed that considerable amounts of fibrinogen remain in the serum separating after gross coagulation has taken place. They have therefore concluded that heparin interferes with the polymerization of fibrin, and in a study carried out at the Jewish Chronic Disease Hospital, Brooklyn, New York, have utilized this property in the investigation of the possible presence of polymerization-accelerators in the serum in various diseases. The method is described in detail. Blood is drawn one hour after the intravenous injection of 50 mg. heparin (or the heparin is added in vitro, 8 μg. to 3 ml. blood) and clotted at 37° C. in four tubes in aliquots of 3 ml. each, 0·3 ml. 0·1 M sodium citrate being added to the clotted blood at hourly intervals and the clot centrifuged down immediately. The supernatant serum is then investigated for the presence of fibrin, using the photo-electric prothrombin-time method, and the fibrinogen concentration is measured by determination of the density of the clot.

These tests were performed on the serum of twelve normal persons and of a number of patients with rheumatoid arthritis, rheumatic fever, and a variety of other clinical conditions, a total of 36 tests in vivo and 54 in vitro being carried out. A positive result was indicated by a complete consumption of fibrinogen. The results were negative in normal subjects, but were positive in active rheumatoid arthritis (22 cases) and active rheumatic fever (five cases). Moreover, these test results remained positive long after laboratory criteria of rheumatic fever had returned to normal and they were not affected by the administration of cortisone. In the tests on serum from patients with such other diseases as glomerulonephritis, lupus erythematosus, or carcinomatosis the results were negative.

The mode of action of heparin is discussed. It is concluded that heparin, in addition to its anticoagulant properties, can delay the polymerization of fibrinogen, and that this action is accelerated in the serum of patients with active rheumatic disease. E. G. L. Bywaters.


In this paper from the Paris Faculty of Medicine attention is directed to changes in the state of the intercellular substance of tendinous and aponeurotic tissues in a variety of lesions, including synovial cysts ("ganglia"), tumours of tendon sheaths, lesions of knee-joint menisci, and Dupuytren's contracture. Of particular importance is the mucopolysaccharide material of the connective-tissue ground substance. The authors describe a histological study of tissue from 23 ganglia (mostly from the dorsum of the hand), sixteen examples of tendon rupture, and fifteen "histiocytic" tumours of tendon sheaths. Sections were stained with haemalum eosin, Masson's trichrome stain, and toluidine blue or methylene blue to show metachromasia, as well as with the last two dyes at varying pH to assess the apparent isoelectric point of tissue constituents. The periodic-acid-Schiff technique was also used.

In all the conditions above referred to the abnormal connective tissue present showed a positive periodic-acid-Schiff reaction, metachromatic staining, and intensified staining with toluidine blue and methylene at a pH of about 3·5.

H. A. Sissons.


The case records of patients attending the out-patient medical clinic of Karolinska Sjukhuset, Stockholm, during the year 1941 were analysed with special reference to the incidence of unexplained elevation of the erythrocyte sedimentation rate (E.S.R.). In addition all cases in which there was a raised E.S.R. or hyperglobinaemia of uncertain origin seen during the period 1941–50 were reviewed.

The over-all frequency of such cases was low. Only about 0·3 per cent. of the out-patients seen during 1941 showed even a transitory unexplained rise in E.S.R. and in most cases this could be attributed to various infections. The very small number of cases of cancer presenting as a vague illness with a high E.S.R. is stressed. The authors consider that electrophoretic analysis of the serum proteins is of diagnostic value. Although malignant tumours do not produce any specific serum protein pattern, a rise in the α-globulin and fibrinogen values is suggestive. A raised γ-globulin value on the other hand is more suggestive of hepatic cirrhosis, collagen disease, or myeloma.

Among 790 out-patients (out of a total of 9,140 seen in 1941) in whom the E.S.R. was shown to be raised, only 32 had insufficient signs and symptoms to make a diagnosis possible at the first attendance. Of these, nine were subsequently found to have a permanently raised E.S.R. which, over a period of observation of 9 to 13 years, was unassociated with any manifestation of disease. This figure of nine was brought to a total of 37 after analysis of in-patient and out-patient records for the period 1941–50. In all but two of these cases following fourteen of the 35 cases the raised E.S.R. could be definitely or probably attributed to disease. In the remaining 21 the benign nature of the elevated E.S.R. was supported by the results of clinical and laboratory investigations carried out over periods ranging from 3 to 20 years. All but one of these patients were females.

Electrophoretic studies of the plasma protein patterns showed that four main types of plasma protein disturbance were distinguishable:

(1) Serum hypergammaglobulinaemia (nine cases);
(2) Increased plasma β-globulin and fibrinogen values (five cases);
(3) Decreased plasma α1-globulin values (four cases);
(4) Increased plasma α2-globulin values (three cases).

Related studies were re-examined with this knowledge, with the aim of elucidating the mechanisms underlying the increase in the sedimentation rate.
(3) Increased plasma fibrinogen value (five cases); and
(4) the presence of abnormal protein components (two cases).

A. Brown.


Reaction to Diphenylamine in Rheumatology. (La reazione alla difenilamina in reumatologia.) Rivano, R., Solari, S., and Capponi, G. (1955). Reumatismo, 7, 294. 2 figs, 8 refs.


Electrophoretic Studies of the Serum Proteins in Acute Rheumatism. (Rilevii elettroforetici sulla disproporzione dell'infezione reumatica acuta.) Antonaci, B. L. (1955). Reumatismo, 7, 229. 4 figs, bibl.


ACTH, Cortisone, and Other Steroids


In this interesting article from the Deaconess Hospital, Great Falls, Montana, the authors report the apparently paradoxical action of ACTH (corticotrophin) in 21 cases of chronic congestive heart failure with persistent oedema. The cases comprised eight of arteriosclerotic heart disease, three of hypertensive heart disease, eight of rheumatic heart disease, and two of cor pulmonale.

Despite the usual diuretic regimen, which included the administration of ammonium chloride and mercurial diuretics and other relevant treatment, these patients were not losing their oedema.

While this diuretic regimen was continued ACTH was given in doses of 10 to 25 mg. 6-hrly for 10 to 12 days. The results were remarkable in that some patients lost as much as 17.5 kg, body weight in 13 days. Three types of response were noted:

(1) A spontaneous diuresis after 4 to 6 days;
(2) A profuse diuresis after the ACTH had been stopped; and
(3) A greatly improved response (in ten of the cases) to mercurial diuretics during or after the administration of ACTH.

The treatment failed in four patients of which three were cases of rheumatic heart disease. In some cases there was an initial slight increase in the oedema.
ABSTRACTS


The authors point out that since 1895, when de Quervain first described the stenosing tenosynovitis at the radial styloid process with which his name is associated, of the many methods of treatment which have been suggested, operation alone has hitherto achieved success. Various types of injection tried in the past have given poor results, but in view of the reported success of local injections of hydrocortisone in the treatment of "tennis elbow" and other soft-tissue lesions it was decided to undertake a controlled trial of this method in twenty consecutive cases of de Quervain's disease seen at the Middlesex Hospital, London.

The patients were divided into two groups. Group A received 25 mg. hydrocortisone injected into the tendon sheath after infiltration with 1 ml. 2 per cent. procaine solution, and Group B received an injection of procaine alone.

Of the ten patients in Group A, seven experienced complete relief of symptoms for 100 days or more, whereas no patient in Group B experienced relief for more than 2 days. When patients in the latter group were later treated with hydrocortisone, nine of the ten lost their pain for a substantial period. Oswald Savage.


In a search for a preparation capable of prolonging the local palliative effect of the intra-articular injection of hydrocortisone in inflammatory arthritic conditions the authors tried the effect of a micro-crystalline suspension of a less soluble ester of hydrocortisone, namely, hydrocortisone tertiary-butylacetate. At the University of Pennsylvania Hospital, Philadelphia, 92 patients with rheumatoid arthritis and 79 with osteo-arthritis of one or both knees (who had previously been treated with intra-articular injections of hydrocortisone acetate) were given, without their knowledge, the new ester instead in identical dosage.

A comparison of the results in the two periods of treatment showed that the new ester produced an amelioration which was greater and of longer duration in about 60 per cent of the total of 171 cases; in about 5 per cent. hydrocortisone acetate was considered more effective, and in the remaining 35 per cent. there was no appreciable difference between the effect of the two hormone preparations. The most significant differences were noted in the patients with osteo-arthritis. There was an exacerbation of the joint symptoms in three patients after the injection of hydrocortisone tertiary-butylacetate and in four after hydrocortisone acetate, but no other complications were encountered.

K. C. Robinson.


It is first pointed out that in the treatment of acute adrenal insufficiency, when it is necessary rapidly to raise the level of circulating hormone, intravenous

In conclusion the authors speculate on the possible mode of action of ACTH in these circumstances and suggest that it may inhibit the release of a DOCA-like, sodium-retaining hormone from the adrenal cortex, or alternatively, that it may have some direct action on the failing myocardium.

G. S. Crockett.


The results obtained with short-term courses of corticotrophin (ACTH) or cortisone in 64 children aged 1 to 9 years with the nephrotic syndrome are reported. No significant difference between the effects of the two drugs was noted. An over-all incidence of diuresis of approximately 80 per cent. in 153 courses of ACTH or cortisone was obtained, diuresis occurring rather more frequently during administration of the drug than after withdrawal. The incidence of diuresis was lower in children in whom the disease later progressed to renal failure, even although there was no indication at the time of progressive renal disease. No attempt was made to distinguish cases of pure nephrosis from those of nephrotic nephritis, but patients with fixed azotemia or persistent hypertension were excluded.

Of the 64 children, 43 required only three courses of treatment, the total stay in hospital of these being 1 to 1½ months. However, although morbidity was much reduced by administration of these drugs, the mortality rate was not significantly improved; seventeen patients died, fourteen of them in renal failure.

Margaret D. Baber.


The pathological changes associated with peri-arthritis of the shoulder are discussed and it is pointed out that theoretically such a condition should respond to cortisone or hydrocortisone. However, the previously reported results of hormonal treatment have varied widely.

The present authors, working at Guy's Hospital, London, have improved their own results by changing their technique of injection slightly. They now introduce hydrocortisone at three different points: anteriorly into the subacromial bursa, antero-laterally into the long head of the biceps, and posteriorly into the joint capsule, injecting 50 mg. hydrocortisone in a 2-ml. suspension with the addition of 1,000 units hyaluronidase and 2 to 3 ml. 2 per cent. procaine.

Of fifty acute cases treated by this method, 36 (72 per cent.) progressed to complete recovery in 7 to 14 days and eleven (22 per cent.) were improved.

Of 23 chronic cases of the "frozen-shoulder" type, thirteen (56 per cent.) regained full function in 4 to 6 weeks after injections of hydrocortisone and shoulder exercises, and five (22 per cent.) were improved.

Oswald Savage.
administration of hydrocortisone is much more effective than intramuscular. Though it has no advantage over oral administration of cortisone, which is followed within an hour by a significant rise in the plasma level of 17-hydroxycorticosteroids, it may be of great value in the patient who is unconscious or vomiting. The author describes the results of intravenous infusion of hydrocortisone in two cases of Addisonian crisis, one case of acute adrenal insufficiency during adrenalectomy, one of adrenal insufficiency after operation following prolonged cortisone therapy, in one of severe post-operative shock, and in one of Cushing's syndrome as a diagnostic test to distinguish between adrenal tumour and hyperplasia.

In the two cases of Addisonian crisis the results were disappointing, and this is attributed partly to the fact that the solution was made up in 5 per cent. glucose and not normal saline and partly to the fact that no additional cortisone was given by mouth or intramuscular injection. Hydrocortisone for intravenous use is supplied in ampoules containing 100 mg. in 20 ml. 50 per cent. alcohol, this being added to 0.5 or 1.0 litre of an isotonic fluid. Usually the Addisonian crisis is associated with sodium depletion and the diluent should therefore be normal saline. Since the effect of intravenous hydrocortisone is transient, the level of circulating hormone falling rapidly at the end of the infusion, it is necessary to give cortisone intramuscularly as well and to continue the infusions until this becomes effective or oral administration is possible. The author suggests the following regimen for the treatment of patients in Addisonian crisis. If the patient can take cortisone by mouth 100 mg. should be given every 4 hours until improvement is obvious; in other cases 100 mg. cortisone should be given intramuscularly and an infusion of hydrocortisone in normal saline begun. For the first 2 hours the rate of infusion should be 25 mg. an hour; subsequently it should be 12.5 mg. an hour. The infusion should be continued for at least 8 hours, and as soon as possible cortisone should be given by mouth. In cases in which the plasma potassium level is very high an intramuscular injection of 5 to 10 mg. deoxycorticosterone is advisable.

Acute adrenal insufficiency in which there is no sodium depletion may occur during operation or when a patient with adrenal atrophy is subjected to severe stress. Two such cases are described, in both of which there was a satisfactory response to intravenous infusion of hydrocortisone in 5 per cent. glucose.

Rukes and others (Metabolism, 1954, 3, 481) reported cases of severe surgical shock uninfluenced by blood or plasma transfusion or by noradrenaline which responded to intravenous infusion of hydrocortisone. In one case of this type in the present series benefit was only temporary. The author suggests that the use of hydrocortisone in such cases merits further investigation. Kenneth Stone.


This paper from the University of Leeds records the authors' experience with corticotrophin (ACTH) administered by slow intravenous infusion in the treatment of rheumatic conditions. Between August, 1951, and October, 1953, 425 patients, of whom 329 suffered from rheumatoid arthritis of all grades of severity, were treated in this way, other accepted methods of treatment being employed as necessary at the same time. Variations ranging from 5 mg. to 25 mg. were made in the dose of ACTH given in each infusion until it was clear that 20 or 25 mg. gave the maximum effect. After preliminary trials of various vehicles the majority of patients received hormone in one litre of normal saline, and it was found that the optimum duration for each infusion was 18 to 24 hours. Generally the practice was to administer three infusions at intervals of 4 to 7 days during each admission to hospital, lasting usually from 2 to 4 weeks. In a total of 1,490 infusions no serious complication arose, the most frequent being the development of local venous thrombosis, which made subsequent treatment difficult.

Among those patients who benefited by the treatment, the majority experienced a striking improvement after the first infusion which was maintained, but not increased, by subsequent infusions. Euphoria was induced in most cases and the authors regard this as a valuable contribution to the rehabilitation programme in patients who are depressed and apathetic. A sense of increased physical well-being, improvement in appetite, and the dissipation of malaise were also marked. Altogether, some degree of improvement was obtained in 89 per cent. of cases of rheumatoid arthritis, the greatest change being in the functional capacity. Analysis of the results showed that the most improvement occurred where the disease had been present for less than one year. On the other hand the degree of improvement obtained was much the same in all age groups. Oswald Savage.


Studies at the University of North Carolina have shown the eosinophil count to be superior to other commonly used indices of adrenocortical response to single injections of ACTH. The present study was designed to provide the basis for a more detailed analysis of the factors influencing the eosinophil response to both ACTH and cortisone. To twenty healthy male dental students ACTH was given intramuscularly in doses of 5, 10 and 20 U.S.P. units, and cortisone acetate was given orally in doses of 12.5, 25, and 30 mg. In every case the drug or a control saline injection was given at noon, and eosinophil counts were made at 8 a.m., noon, and 4 p.m. There was an interval of at least one week between successive tests, each subject being tested twice at each dose level of ACTH and cortisone.

The threshold dose for intramuscular ACTH was found to be less than 5 units and for oral cortisone less than 12.5 mg. For ACTH, in the dose range 0 to 10 units, the eosinophil response was found to distinguish between doses differing by 5 units, and in the dose range
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10 to 40 units to distinguish doses differing by 10 units. The author points out that the minimum difference in dose detectable in this way increases with increasing dose because of the asymptotic approach to complete depression of the circulating eosinophil count. The minimum difference in dose that could be detected in the case of cortisol was of the order of 12-5 mg. over the whole range of 0 to 50 mg., the dose–response relationship being almost perfectly linear over this range.

In discussion the author suggests that from these findings it would appear that the eosinophil response to hormonal stimulus is not merely superimposed upon a diurnal trend, but that the diurnal trend is actually abolished by the administration of hormone. Thus, strict standardization of tests to correct for directional changes in the eosinophil count during the period before testing does not appear to be necessary.

Adrian V. Adams.


The effect of corticotrophin and of cortisone on the excretion of 17-ketosteroids was studied at King’s College Hospital Medical School, London, in twelve patients with normal or hypo-adrenal function. Corticotrophin produced a rise in the excretion of the 11-oxy-17-ketosteroid and β-fractions in patients with low adrenal activity, but gave variable results in patients with normal adrenal function. After administration of cortisone there was general depression of the total 17-ketosteroid excretion with a rise in excretion of the 11-oxy-17-ketosteroid fraction.

F. W. Chattaway.


The study here described from the University of North Carolina Medical School, Chapel Hill, N.C., was carried out on nine healthy male students and was designed to compare the value of haematological and urinary changes as indices of the response of the adrenal cortex to the injection of small, graded doses of ACTH (corticotrophin). The ACTH was given at noon in doses of 5, 10, 20, and 40 U.S.P. units by intramuscular injection, and blood samples for determination of the leucocyte count were taken at 8 a.m., noon, and 4 p.m., and urine collected over three 4-hr periods, 8 a.m. to noon, noon to 4 p.m., and 4 p.m. to 8 p.m., for analysis of sodium, potassium, uric acid, and 17-ketosteroid content. No attempt was made to control the diet or activities of the subjects, but no subject with recent exposure to stress (for example, a dental extraction or immunization procedure) was included in the study and an interval of at least one week was allowed between two consecutive tests on the same individual.

The changes in the leucocyte count were related approximately, but not linearly, to the dose of ACTH given, that in the number of eosinophil granulocytes being the most closely correlated. The 4-hr eosinophil response is therefore recommended as the most suitable for determining quantitatively the response to small doses of ACTH or single acute stresses. The variability of the response as determined by changes in the sodium, potassium, and 17-ketosteroid excretion in the urine and the uric acid : creatinine ratio is discussed. It is concluded that these urinary indices lack the specificity necessary for determining quantitatively the adrenocortical response to small, graded doses of ACTH.

Adrian V. Adams.


9-α-fluoro hydrocortisone has been reported to have twenty times the therapeutic potency of cortisol and about one-tenth of the sodium-retaining power of aldosterone, and has been shown to have an inhibitory effect on the normal adrenal cortex. Because the breakdown products of cortisol and hydrocortisone are essentially like those occurring naturally in the urine and plasma, it is impossible to assess the inhibitory effect of cortisol on the normal or hyperplastic adrenal cortex by determination of the excreted adrenal steroids; this, however, does not hold for 9-α-fluoro hydrocortisone, the breakdown products of which are different from those derived from hydrocortisone. Taking advantage of this fact the authors have observed the inhibitory effect of 9-α-fluoro hydrocortisone in a typical case of Cushing’s syndrome, in which the diagnosis was later confirmed by laparotomy. Adrenal function was assessed by the measurement of the daily excretion of 17-ketosteroids, 17-ketogenic steroids, and hydrocortisone. They found that on administration by mouth of a daily dose of 5 mg. 9-α-fluoro hydrocortisone (equivalent to about 100 mg. cortisol) hydrocortisone excretion was reduced by 50 per cent., and with a dose of 15 mg. daily by 80 per cent. The output of hydrocortisone returned to its previous high level when the drug was withdrawn. The excretion of 17-ketosteroids and ketogenic steroids was uninfluenced.

From all available evidence it appeared likely that the new steroid had suppressed the production of hydrocortisone by the adrenal cortex. It is considered that this action is probably analogous to that of cortisol in the adrenogenital syndrome, in which cortisol suppresses excessive ketosteroid excretion if this is due to hyperplasia, but not if it is due to tumour formation. By the use of 9-α-fluoro hydrocortisone it might, therefore, be possible to differentiate between Cushing’s disease due to cortical hyperplasia—as was probably the case in the patient studied—and that due to tumour.

The authors conclude that the inhibitory effect of this steroid is mediated through the pituitary gland by a sudden increase in the plasma concentration of hydrocortisone-like substances.

J. N. Harris-Jones.

9-α-fluoro hydrocortisone causes an increase of the body fluids (intra- and extracellular) with retention of water, chlorides, and sodium and increased potassium excretion (Na : K being increased). (Incomplete) studies of the carbohydrate metabolism seem to show a diminished sensitivity to insulin. The blood eosinophil count shows no definite change. The excretion of urinary 17-ketosteroids is much diminished. The adrenal function is depressed, even after only short treatment.

Prednisone produces an increase in the urinary sodium excretion and diuresis without obvious alteration of the plasma electrolytes. The effect on carbohydrate metabolism is not convincing, but perhaps slightly diabetogenic. The eosinophil count is diminished, the urinary 17-ketosteroid excretion decreased. There is little influence on the excretion of uric acid in gouty subjects, although clinically the result was equal to that of phenylbutazone and was excellent in one case. Adrenal function is depressed.

There does not seem to be any causal relation in the case of either steroid between its influence on the mineral and carbohydrate metabolism and its effect on the signs of inflammation and its antiphlogistic action.

V. C. Medvei.


At the Institute of Clinical Medicine and Therapeutics of the University of Modena, eight patients with a variety of conditions were treated with prednisone ("Deltacortene") and its effects carefully evaluated. The cases included one of adrenal virilism, two of rheumatoid arthritis, one of ankylosing spondylitis, three of bronchial asthma, and one of lupus erythematoses with arthritis. The drug was given by mouth in three or four doses daily, the total dosage on the first day being 35 mg., followed by 30 mg. for 3 days, 20 mg. for 3 days, 15 mg. for 4 days, and 10 mg. thereafter. The period of treatment ranged from 10 to 35 days. A dosage of less than 10 mg. daily did not appear to be effective.

Clinically, the results of treatment were satisfactory in all cases and much superior to those obtained with cortisone—for example, the patient with adrenal virilism started menstruating after 12 days compared with 45 days with cortisone in doses three times greater. One of the patients with asthma, who had an active duodenal ulcer in addition, was able to continue treatment with prednisone, whereas the administration of ACTH or cortisone had caused severe epigastric pain and had had to be discontinued. The drug's marked diuretic effect was confirmed; it was noticeable in the first 4 to 6 days of treatment and was accompanied by increased urinary excretion of chlorides. No other side-effects were observed.

Laboratory investigation of the endocrine effects showed that after 7 days there was a considerable reduction in the urinary excretion of 17-ketosteroid and a modest increase in that of 11-oxytocorticoids; the urinary excretion of gonadotrophins was unchanged. Studies of renal function indicated that there was an increase in glomerular filtration and a decrease in tubular re-absorption of water. Blood coagulation was not affected. After 15 days' treatment the serum globulin content had become normal in one patient with rheumatoid arthritis, and an increase in the serum cholesterol level was noted in six other patients.

The effects of prednisone on the urinary steroid and gonadotrophin excretion suggest that it acts in part by a suppressive effect on the anterior lobe of the pituitary gland.

V. C. Medvei.


In the treatment at Buffalo (New York) General Hospital of eight patients with severe bronchial asthma which had been satisfactorily controlled by cortisone or hydrocortisone in doses of 30 to 70 mg. per day, these drugs were replaced experimentally by 9-α-fluoro hydrocortisone, which was given orally in a dose of 2 to 4 mg. daily (in one case 8 mg.). All the patients got rapidly worse [as would be expected with such a minute dose, which would be more suitable as a placebo] and it was concluded that the substance is of no value in allergic disorders.

The effect of the new synthetic corticosteroid "Meticorten" (Metacortandracin, prednisone) was then studied in twenty asthmatic patients most of whom had been maintained for some time with cortisone, hydrocortisone or ACTH, a dose of 5 mg. Meticorten being substituted for each 20 mg. hydrocortisone or each 25 mg. cortisone. Of the sixteen cases in which the treatment was so changed, in fifteen the condition was well controlled by the new drug, of which the average maintenance dose required was only 10-2 mg. per day compared with 53-1 mg. cortisone and 41-6 mg. hydrocortisone. Treatment had to be interrupted in one case because of severe epigastric pain which, however, disappeared when Meticorten was discontinued. One patient who had not previously received cortisone was well maintained on 10 to 15 mg. Meticorten per day; however, two other patients, one with perennial rhinitis and one with giant urticaria, derived no benefit. In six cases in which cortisone or hydrocortisone had caused water retention this disappeared when Meticorten was substituted. No increase of blood pressure was observed in any of the patients treated with Meticorten. It is concluded that Meticorten is, weight for weight, three to four times as effective as hydrocortisone, and four to five times as effective as cortisone.

H. Herxheimer.
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At the Medical Clinic of the University of Genoa, metacortandracin (prednisone) was tried in the treatment of 21 patients, twelve of whom were suffering from rheumatoid arthritis, one from gouty polyarthritis in a subacute phase, one from early scleroderma, six from osteo-arthritis with acute pain, and one from the "shoulder-hand" syndrome following myocardial infarction, with swelling of the hand and sub-ankylosis of the shoulder. In the six cases of osteo-arthritis the patients' age and sex were not given; of the remainder, seven were men and eight women, their ages ranging between 17 and 75 (but mainly between 30 and 60). Only the short-term results (up to 30 days) are reported and the effect of interruption of the treatment was not studied.

Metacortandracin was found to have an anti-rheumatic effect four to six times greater than that of cortisone and to be more effective than hydrocortisone. It did not show any influence on water and salt metabolism except for a very slight diminution in the serum potassium level. In two cases there was an initial increase of the blood pressure, which returned to normal when the dosage was reduced. The dosage (in rheumatoid arthritis) was as follows: 20 mg. daily (in four doses) for the first 3 days; 15 mg. for the next 3 days; 10 mg. for 10 days; 7.5 mg. for 4 days; and 5 mg. daily thereafter as a maintenance dose. In no case was epigastric pain, acne, erythema, or psychological disturbance observed. A very slight degree of moon-face developed in two cases, and excessive perspiration in one.

The introduction of Metacortandracin is, in the opinion of the authors, a real step forward in the steroid treatment of rheumatic disorders.

V. C. Medvei.


The authors have investigated the effect of ACTH on gastric secretion in five healthy medical students with no radiological evidence of peptic ulcer who were given 25 units ACTH (corticotrophin) every 12 hours for 6 days. This produced an adequate adrenal response in all the subjects, as shown by a rise in the 17-hydroxy-corticoid excretion and a fall in the circulating eosinophil count.

Analysis of the aspirated gastric juice showed a marked fall in viscosity, a slight fall in the volume of total gastric secretion, a moderate increase in concentration of pepsin, and a slight increase in concentration of acid; the absolute amounts secreted showed little change. The blood pepsin level also showed little change, but the urinary pepsinogen excretion increased greatly. It is pointed out that this must have been due to renal and not to gastric factors and that in the circumstances of the experiment, and even under basal conditions, urinary pepsinogen excretion is a very unreliable guide to gastric pepsin secretion.

Of particular interest are the authors' observations on a sixth medical student on whom several previous gastric tests had been carried out for research purposes with no untoward results. On the present occasion after 90 hours of ACTH administration he developed epigastric pain, vomiting, and gastric distension. Radiography revealed the presence of a post-bulbar duodenal ulcer—

which had disappeared on re-examination 26 days later. There had been no observed rise in acid or pepsin secretion before the development of symptoms, although these values did increase later, suggesting that increased gastric secretion is not a cause but a consequence of exacerbation of duodenal ulcer. On the other hand the content of visible mucus and the viscosity of the gastric juice fell to a greater extent in this subject under the influence of ACTH than they did in any of the other five subjects. The authors suggest that changes in the properties or in the rate of production of gastric mucus may be of importance both in the exacerbation and healing of peptic ulcer.

T. D. Kellock.


In this study of the antipyretic action of cortisone, carried out at Washington University School of Medicine, St. Louis, fever was induced in male rabbits weighing 2.5 to 3.5 kg. by means of "Pyronen", a highly purified polysaccharide from a species of Pseudomonas, or by native dextran with an average molecular weight of between 200,000 and 300,000, or by injecting typhoid vaccine. One group of animals received 25 mg. cortisone twice daily for the 3 days preceding the experiment, another group remaining untreated as a control. On the day of the experiment the treated group received a further injection of 25 mg. cortisone, and both groups were then given pyrogen. In both groups there was a transient fall in the leucocyte count, but only the control group showed a significant rise in temperature. In a repetition of the experiment using dextran as the pyogen, a similar result was obtained.

Two experiments were then carried out to test whether the serum factor (known to be involved in the action of pyrogens) was affected by cortisone:

In the first, typhoid vaccine incubated with serum from cortisone-treated rabbits was injected into rabbits made tolerant to this pyrogen. The latent period of the response was identical with that in tolerant rabbits given typhoid vaccine incubated with normal serum, thus showing that pretreatment of an animal with cortisone did not eliminate the serum factor.

In the second experiment the injection of typhoid vaccine incubated with normal serum did not produce fever if the rabbits had previously been treated with cortisone.

The authors conclude that the antipyretic effect of cortisone does not involve the leucopenic reaction nor the fever-accelerating factor present in the serum.

P. A. Nasmyth.

Recently two potent and atoxic corticosteroids have been synthesized: prednisone and prednisolone. They are two to four times as active as cortisone and hydrocortisone; on the other hand they induce less potassium excretion and very little sodium retention in therapeutic dosage. The authors confirmed their anti-inflammatory properties in fifteen rabbits with uveitis induced by horse-serum. 54 patients with various ocular inflammations were treated with the new steroids and several showed dramatic responses even where other steroids were ineffective. They were found to be more potent in ophthalmological conditions than were cortisone or hydrocortisone.

S. J. H. Miller.


The literature of this rare disease is reviewed. The lesions are typically a symmetrical thinning of the temporal side of the sclera of each eye, with a well-marked margin. Uncommonly it may perforate, more usually the uvea may bulge the conjunctiva which covers it. There is a marked association with polyarticular rheumatism. The author suggests there may be an analogy between the condition and osteomalacia of pregnancy and that calcium, phosphorus and vitamin D should be added to the diet.

Lorimer Fison.


The characteristic clinical picture which is observed following abrupt withdrawal of cortisone after prolonged administration is described. At the Massachusetts General Hospital nineteen patients with chronic asthma received cortisone for periods varying from 11 to 38 months (average daily dose 40 to 100 mg.). Between 24 and 48 hours after the last dose headache, nausea, vomiting, and restless development, with generalized malaise and, in several instances, tender muscles and marked arthralgia. Symptoms became more severe for several days and then rather promptly lessened, disappearing entirely without treatment after 2 to 5 days. In general, the longer the duration of cortisone administration, the more severe were the symptoms on cessation of treatment.

The alarming clinical state of these patients was not associated with any significant changes in vital signs or in the responses to laboratory tests. The cause of the withdrawal syndrome is not at the present clear. When six of the patients were given an intravenous infusion of 500 ml. 0.9 per cent. saline solution daily for 1 to 3 days their symptoms were somewhat ameliorated, suggesting that adrenal insufficiency might be a cause. Asthma returned in a severe form necessitating resumption of cortisone therapy after an average of 8 days in those patients who did not receive saline infusions and after an average of 26 days in those given saline. Thus in all cases asthma returned only after the withdrawal symptoms had spontaneously cleared.

[This withdrawal syndrome is also observed in some patients given cortisone for rheumatoid arthritis, so it is not necessarily confined to allergic patients.]

G. B. West.


The study here reported from the Institute of Medical Hydrology, Milan, was undertaken in order to clarify the relationship between osteoporosis and osteomalacia (a subject of much controversy) and to evaluate the role of the adrenal cortex in the metabolism of protein in these osteopathies. It was carried out on nineteen cases of senile osteoporosis and ten cases of osteomalacia, nine subjects who showed no radiological evidence of decalcification serving as controls. Nearly all the 38 subjects were women, ranging in age from 54 to 93 years, who had been admitted to hospital suffering from chronic disease; all patients in whom there was clinical evidence of hepatic or renal insufficiency were excluded from the study.

Estimation of the serum concentrations of calcium, phosphorus, alkaline phosphatase, total protein, albumin, alpha, beta, gamma, and total globulin, and measurement of the urinary excretion of calcium, 17-ketosteroids, and 11-corticosteroids all gave results which fell within the normal range. The conclusion is therefore drawn that "too sharp a distinction... has been made between osteoporosis and osteomalacia".

[This investigation failed to achieve its aims. No balance studies were performed and no details of intake or excretion of the various metabolites are given. The method employed can give only very limited information, which is insufficient to justify the authors' conclusion.]

P. D. Bedford.


Ann. Allergy, 13, 252. 2 figs, 12 refs.

The authors report from the Mount Sinai Hospital, Minneapolis, two cases of perianal bronchial asthma in the first of which severe lumbar pain appeared after 3 years' continuous therapy with cortisone (dosage 50 to 100 mg. per day) or ACTH gel (20 to 40 mg. per day). Radiological examination revealed osteoporosis of the lower dorsal and lumbar vertebrae and pelvis, and multiple compression fractures of the lumbar vertebrae; the mean urinary calcium excretion was 194 mg. per day. The second patient had received maintenance doses of 50 to 75 mg. cortisone per day. After 3 years of this treatment the urinary calcium level was 474 mg. per day,
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and radiographs of the spinal column showed early osteoporotic changes. In this case the patient had not complained of pain.

In both cases combined treatment with oestrogens and androgens was started at once. In the first patient this was followed by the disappearance of the pains, but the radiological picture remained unchanged; no results are reported for the second case. [The cortisone treatment was apparently continued in both patients, although the authors do not say so.] H. Herxheimer.


Other General Subjects


Four cases of gastro-intestinal haemorrhage following the administration of phenylbutazone are reported.

(1) In the first the patient had an extremely painful neuralgia in the left cervico-brachial region (subsequently shown to be due to neoplastic destruction of a cervical vertebra). Treatment, which included 500 mg. phenylbutazone given by intramuscular injection daily, produced much relief of the pain, but after 2 weeks the patient developed severe melena, shock, and severe anaemia, which persisted in spite of blood transfusions. After a haematemesis 2 weeks later, gastric and duodenal ulcers were demonstrated radiologically and the patient died after gastrectomy.

(2) The second patient was treated for rheumatoid arthritis with phenylbutazone in a daily dose of 400 mg. by mouth for 11 days, followed by 600 mg. daily for another 2 weeks. This improved the condition considerably, but was followed by a haemorrhage of fresh blood per rectum which stopped immediately on withholding phenylbutazone. Proctoscopy and radiological examination of the gastro-intestinal tract revealed no abnormality. Two weeks later aspirin was given for a recurrence of the arthritic pains and a similar haemorrhage occurred without any subsequent ill-effects.

(3) The third patient developed melena after receiving phenylbutazone intramuscularly for lumbar osteoarthritis in a dose of 1 g. every 2 days for 20 days; it was not possible to determine the source of the haemorrhage.

(4) The fourth patient was treated for sciatica with phenylbutazone in a daily dose of 800 mg. by mouth. After 10 days of treatment blood appeared in the stools and the patient complained of severe gastric pain. X-ray examination showed signs of gastritis which cleared up when treatment with phenylbutazone was stopped.

In an attempt to elucidate the effect of phenylbutazone on the gastro-intestinal tract the stools of 41 patients suffering from various types of rheumatic and arthritic conditions were tested for blood by the amidopyrine method after oral treatment with phenylbutazone in daily doses of 0.4 to 1 g. for an average period of 49 days. Whereas in all cases the test had given negative results before treatment, a positive result was obtained repeatedly after treatment in fifteen cases and intermittently in eleven others. The occurrence of blood appeared to be related to the duration of treatment in most cases, but in some blood was present after a relatively short course of treatment.

Although the authors admit that pre-existing factors may have determined the occurrence of severe haemorrhage in the four cases described, it would appear probable from their later experimental findings that some action of phenylbutazone was at least a contributory factor.

R. Wien.


It was found by the authors that gastric lesions could be produced experimentally in the rat by giving daily doses of 100 mg. phenylbutazone per kg. bodyweight, either by mouth or by injection, after ligating the pylorus. These lesions, which appeared about the sixth day, took the form of small, diffuse ulcers, often haemorrhagic, originating in the mucous glandular layer and extending towards the surface. Concomitantly there was a considerable fall in the hydrochloric acid content of the gastric juice, resulting in some cases in achlorhydria. Analysis of the gastric juice showed that little phenylbutazone was excreted by this route.

The lesions produced clinically and experimentally by phenylbutazone are contrasted with those associated with the clinical administration of cortisone and ACTH. The latter occur in the duodenum rather than the stomach, and are the result of increased gastric secretion and hyperchlorhydria, whereas the appearance of the experimental lesions suggests that phenylbutazone has a direct toxic action on the gastric mucosa. There is thus little support for the suggestion that the gastric effects of phenylbutazone treatment are due to stimulation of the adrenal cortex.

R. Wien.


Among the patients included in a large survey of rheumatic disease carried out in Germany in 1936–37, there were 73 pairs of twins. In fourteen of the 43 pairs of identical twins both members suffered from rheumatic disorders, whereas of the thirty pairs of non-identical
twins in only two were both members affected. In the author's view these findings demonstrate the fortuitousness of rheumatic infections and the importance of trigger mechanisms. The more frequent involvement of both twins in the identical series is taken as affording evidence of a hereditary disposition to rheumatic disorders. Further analysis showed that even the type and progress of the disease was influenced by heredity. The time interval between the onset of rheumatic disease in two members of a pair was sometimes many years and in only a few cases did the onset coincide. Re-examination of 28 of the pairs in 1951–52 showed that one further pair in each group had become concordant.

G. W. Csonka.


Ocular manifestations of chronic rheumatism are similar to those due to any evolutive infection. They are described in children's chronic rheumatism, evolutive polyarthritis, and ankylosing spondylarthritis. In all cases, iridocyclitis may be torpid and revealed by routine eye examination.

S. Vallon.


Abstracts

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