**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**

**Natural History of Rheumatic Heart Disease in the Third, Fourth, and Fifth Decades of Life.**

I. Prognosis with Special Reference to Survivorship.  

The natural history of rheumatic heart disease in the third, fourth, and fifth decades of life, with special reference to survival, was studied at the New York Hospital-Cornell Medical Center in the case records of 757 patients out of a total of 1,042 coming under observation since 1916. There were 430 females and 327 males, and at the time of the last follow-up about three-fifths were 30 years of age or over, one-third were over 35, and one-seventh were aged 40 or more. During the period of observation there were 78 deaths in patients who had reached the age of 20–53 from cardiac causes, eight from bacterial endocarditis (before the introduction of antibiotics), and seventeen from other causes or from accidents. The diagnosis was established before the age of 20 years in nearly all the cases, and less than 3 per cent. had recurrent carditis after that age. In four-fifths cardiac enlargement was moderate (not detectable clinically) and in one-fifth it was marked.

Mitral insufficiency was diagnosed in 392 patients. Carditis without other major rheumatic manifestation was observed in one or more attacks in only one-fifth of this group, and was associated with polyarthritis, chorea, or both in about three-fifths. Subcutaneous nodules were observed in 3 per cent. In all except one, cardiac enlargement was moderate. Of twelve deaths in this group, eleven were due to non-cardiac causes and one to bacterial endocarditis. Over the years the murmur regressed in two-thirds of the cases. The over-all average annual mortality was 2.76 per 1,000 compared with 3.1 per 1,000 for the general population. Of the 392 patients, 116 experienced one to five pregnancies.

Physical signs of mitral stenosis and insufficiency, which were present in 269 cases, developed in the majority within 1 or 2 years of an acute attack of carditis. Polyarthritis occurred in one or more attacks in about one-third, chorea in just under one-third, and polyarthritis with chorea in about one-fifth. Subcutaneous nodules were observed in 9 per cent. In only one-fifth of these cases was there marked cardiac enlargement. There were 29 deaths—eighteen from cardiac causes, five from bacterial endocarditis, and six from non-cardiac causes; four patients died 1 to 5 years after mitral valvotomy. The over-all average annual mortality was 7.8 per 1,000; 93 per cent. of the patients survived to the age of 30 years and 86 per cent. to 40 years. Of this group, 112 patients experienced one to five pregnancies.

In 96 patients there were combined aortic and mitral valve lesions, and in 72 of them cardiac enlargement was marked. One or more attacks of polyarthritis occurred in about one-third, chorea in about one-sixth, and polyarthritis with chorea in rather less than one-half. Subcutaneous nodules were observed in one-third, and in "about one-tenth" the carditis was associated with only minor rheumatic manifestations. Of the 37 deaths, 35 were attributed to cardiac causes. The over-all average annual mortality was 29 per 1,000; 75 of the 96 patients survived to the age of 30 but only 38 to the age of 40. A total of fourteen patients in this group experienced one to three pregnancies.

Increasing cardiac involvement was rarely observed in the absence of recurrent carditis. Cardiac enlargement appeared to be a more important factor in prognosis than the type of valvular lesion. The over-all average annual mortality among patients with moderate enlargement was 3.5 per 1,000 compared with 31 per 1,000 among those with marked enlargement. Of the group with moderate cardiac enlargement at the age of 20, 93 per cent. survived to the age of 40, compared with only 40 per cent. of those with marked enlargement. There was no evidence that sex influenced the prognosis.

C. Bruce Perry.

II. Prognosis with Special Reference to Morbidity.  

In this second paper on the natural history of rheumatic heart disease in the third, fourth, and fifth decades, the authors report the results of a follow-up examination...
Acute Chorea in Children and Streptococcal Infection.


This discussion of the relationship between chorea and acute rheumatism is based on a review of thirty cases of chorea in children seen since 1948 at the Clinic for Children's Diseases, Montpellier. Of these cases, seven were examples of "pure" chorea (but two patients in this group subsequently developed recurrences in which signs of rheumatic carditis appeared), and the remaining 23 cases occurred in children with other evidence of acute rheumatism. In twelve cases, polyarthritis and carditis preceded the onset of chorea by periods varying from several weeks to 4 months, in two acute rheumatism occurred simultaneously with the chorea, and in nine at the onset of the chorea there appeared to be an established lesion of the mitral valve.

The authors advance arguments to support the view that chorea represents a peculiar manifestation of a post-streptococcal state and that it occurs some weeks or even months later in the evolution of this state than does acute rheumatism. It is suggested that the rare but occasional occurrence of acute rheumatism and chorea simultaneously may be explained by the assumption that the chorea is the sequel to a first streptococcal infection and the acute rheumatism to a second and later infection. It is argued that this view has important bearings on the treatment and prophylaxis, in that "anti-inflammatory" therapy with salicylates or steroids will be useless in straightforward cases of chorea, but that relapses of haemolytic streptococcal infection must be prevented by the administration of penicillin to all patients with chorea, exactly as to those who have had acute rheumatism.

C. Bruce Perry.


Chronic Articular Rheumatism

(Rheumatoid Arthritis)


At the rheumatism clinic of the Gloucestershire Royal Hospital, Gloucester, the authors have been prescribing prednisone for an increasing number of patients with rheumatoid arthritis. They are careful to point out that the observations reported here are derived not from a controlled clinical trial but from a retrospective study of the treatment prescribed for 167 new patients seen during the last 2 years. It is the practice at this clinic to treat mild cases with aspirin and the usual supportive measures and moderately severe cases with aspirin and topical injections of hydrocortisone; for the severe cases until recently cortisone was prescribed. During the past 2 years eight such cases originally treated with cortisone have been transferred to prednisone, and with increasing experience some milder cases are now treated with prednisone from the beginning. The standard dosage is 5 mg. 8-hrly (15 mg. daily) and the results are assessed in terms of improvement in functional status and of subjective improvement.

Among the 47 cases treated with prednisone there was a considerable movement from lower to higher categories of functional status, sixteen out of thirty women and nine out of seventeen men showing such improvement. Subjective improvement was reported by 43 (90 per cent.) of the patients and this is much higher than "the inevitable
60 per cent.” which is to be expected with any form of
diligent therapy in rheumatoid arthritis. Side-effects
were frequent and of the usual type; the most troublesome
was dyspepsia, which occurred in 23 per cent. of cases,
while obesity was noted in four cases, hypertension in
two, and diabetes in one. The authors consider that
prednisone gives relief from symptoms, that this relief is
sustained, and that the advantages of the treatment
outweigh its not usually severe side-effects.

William Hughes.

Treatment of Rheumatoid Arthritis Complicated by
Chronic Hypercortisonism, and the Theoretical Causal
Role of Certain Amine Oxidases. Scherbel, A. L.,

Since it became generally realized that steroid treat-
ment, if applied to rheumatoid arthritis, must be on a
long-term basis, attention has been called to the clinical
manifestations of chronic overdosage—"hypercortisol-
ism". The undesirable effects to which this is said to
give rise include emotional instability, chronic fatigue,
muscular aching, inability to concentrate, depression of
psychomotor activity, and insomnia. According to the
present authors, when this syndrome is well estab-
lished the withdrawal of corticosteroids may be extrem-
ely difficult, and in certain cases in the past has proved
impossible, even when prolonged over a period of months.
They now report a method of administering a com-
bination of chemotherapeutic agents to patients with
progressive and persistent rheumatoid arthritis whereby
they claim that these difficulties can be overcome or,
when it is used as a routine, are not allowed to arise.
Since patients treated by this method show sustained
improvement despite a decrease in corticosteroid dosage,
they conclude that the disease process is altered signif-
ically by the other drugs used.

The treatment consists in admission to hospital and
administration initially of corticotrophin (ACTH) and
nitrogen mustard (mustine) intravenously to produce
rapid suppression of the basic inflammatory changes in
the joints. Once this has been achieved one of the an-
malarial drugs, chloroquine or hydroxychloroquine, and
small doses of prednisone are given to maintain the
degree of suppression obtained. In addition iproniazid
is administered to alleviate the central nervous mani-
festations which are characteristic of the syndrome, and
possibly to potentiate the effect of the maintenance drugs.
Intra-articular injections of nitrogen mustard and
hydrocortisone are also given every other day when
joint swelling persists. [For details of dosage the
original paper should be consulted.] The patient is
discharged from hospital when the symptoms of hyper-
cortisonism have been suppressed, and continues main-
tenance treatment, under periodic supervision, with
prednisone, iproniazid, and the antimalarial drug,
together with weekly injections of depot corticotrophin,
the dosage of each being gradually reduced.

This method of treatment was applied to sixteen
patients with active rheumatoid arthritis complicated by
chronic hypercortisonism, which had developed as the
result of their having developed resistance to prednisone
and the dose having therefore been progressively in-
creased up to an average of 20 mg. daily. All sixteen are
reported to have improved significantly both objectively
and subjectively, and only one had to abandon the
treatment some weeks after discharge owing to nausea
and anorexia caused by chloroquine. The follow-up
period for six of these patients is now over 2 years.

The authors point out that the symptomatology of
rheumatoid arthritis is characterized both by a mesen-
chymal reaction and by reactions in the central nervous
system, and in the course of an interesting theoretical
discussion they postulate certain biochemical changes as
constituting the basal abnormality in the disease. They
consider that it is the decreased activity of amine oxidases
or the increased peripheral activity of certain amines
that produces hypercortisonism in such patients.

W. S. C. Copeman.

Clinical Course and Corticosteroid Excretion of Patients
with Rheumatoid Arthritis during Long-term Treatment
with Corticotrophin. Savage, O., Chapman, L.,
Robertson, J. D., Davis, P., Popert, A. J., and
7 figs, 9 refs.

In this study, reported from the West London Hospital,
the authors have correlated the clinical course and bio-
chemical findings in 33 female and sixteen male patients
with severe active rheumatoid arthritis who were treated
with corticotrophin (ACTH) for a minimum period of 6
months. The patients were admitted to hospital for 4
weeks for preliminary assessment of the arthritis and
treatment, during which time they were taught the
 technique of self-injection (subcutaneous) and how to
collect and forward to hospital aliquot specimens of the
total daily urine for estimation of 17-hydroxycortico-
steroid (17-(OH)CS) excretion. It was difficult to lay
down an exact dosage as the different batches of corti-
cotrophin differed in strength, this variation being re-
flected in varying levels of 17-(OH)CS excretion and
therapeutic effects. Clinical progress was assessed from
three factors which the authors have found reliable:
(1) erythrocyte sedimentation rate,
(2) strength of grip, measured by means of an
adapted sphygmomanometer,
(3) degree of tenderness to pressure of selected
joints.

It was found that clinical improvement was invariably
associated with increased adrenal activity, as shown by a
rise of at least 50 per cent. in the urinary 17-(OH)CS
excretion. Of the 49 patients, six have had complete
remission of the disease, and in all the others activity of
the disease was suppressed. Side-effects were frequent (all
but three cases) but rarely severe and in only six cases had
the treatment to be discontinued. The complications and
side-effects were those usually encountered during
steroid therapy and included moon face (which was
practically universal), androgenic effects, oedema,
increase in weight, chemosis, and pigmentation. There
was one death from gastro-intestinal haemorrhage; one patient developed hypertension and four developed glycosuria, one of whom became permanently diabetic. In general, however, the authors consider that, under supervision, self-treatment with ACTH for long periods is practicable, that it is suitable for those severe cases which are not improved by other forms of treatment, and has certain advantages over oral cortisone and its newer analogues. The estimation of urinary 17-OHCS excretion is useful in controlling the dosage in long-term cases.

William Hughes.


(Ankylosing Spondylitis)


In this paper from the London Hospital, the authors present the clinical details of six patients, five men and one woman, aged from 42 to 50, in whom chronic inflammatory lesions of the intestines were associated with clinical and radiological evidence of ankylosing spondylitis (although in two cases only the sacro-iliac joints and the symphysis pubis were involved). In four of the six cases the clinical, radiological, and sigmoidoscopic picture was that of chronic ulcerative colitis and in these four cases this disease had been present for some years before the onset of back pain. The one female patient had histologically proved Crohn’s disease and was found, radiologically, to have ankylosing spondylitis involving the sacro-iliac joints and pubic symphysis; she developed chronic ulcerative colitis 2 years later. The 6th patient also had Crohn’s disease and in this case the radiological appearances of ankylosing spondylitis developed in both sacro-iliac joints 9 years later.

The authors consider that the association between ulcerative colitis and ankylosing spondylitis is not fortuitous and suggest that ankylosing spondylitis represents a non-specific reaction to disease of the intestines.

J. Warwick Buckler.


(Miscellaneous)


The authors have investigated the association of osteoporosis and scurvy among the South African Bantu, only patients being selected for study in whom radiography of the spine showed crush fractures or biconcave vertebral bodies in association with osteoporosis for which no obvious cause could be found; those with radiological evidence of only diminished bone density were excluded. During a period of one year sixteen patients (twelve male and four female) at the Baragwanath Hospital, Johannesburg, fulfilled these criteria; all but two of these were under 60 years of age. The results of clinical, radiological, and laboratory studies are presented, together with the post-mortem findings in two patients who died. Liver biopsy revealed gross haemosiderosis in all of seven patients examined and portal fibrosis in six of them; tests of liver function showed that this was grossly abnormal, the albumin:globulin ratio of the serum proteins was reversed, but the serum calcium and plasma phosphorus levels were within normal limits, except in two cases in which the serum calcium level was below normal.

Of the sixteen patients, nine were also suffering from acute scurvy, one had a haemorrhagic pericardial effusion which was considered to be a "scurbitic equivalent", and one had a past history of scurvy; thus eleven patients (69 per cent.) were or had been scurbitic; the remaining five patients presented no evidence of past or present scurvy. The administration of 500 mg. ascorbic acid daily by intramuscular injection resulted in the complete disappearance of the signs of scurvy within 4 to 6 weeks. This treatment, together with 15 g. calcium gluconate daily by mouth, was continued in six patients for a long-term trial; after observation for 9 months to 3 years all except one showed progressive increase of osteoporosis, as judged by further vertebral collapse.

It is generally accepted that a low dietary intake of calcium, abnormal blood protein levels, haemosiderosis, and scurvy are among the factors which, singly or together, may be responsible for osteoporosis. The authors point out, however, that these conditions, with the exception of scurvy, are common to the majority of African patients. In fact both scurvy and osteoporosis are uncommon diseases at this hospital, yet these relatively rare conditions were frequently found in the same patient. Moreover, the incidence of osteoporosis among a group of 48 patients with typical acute scurvy was 18.7 per cent., whereas no case of osteoporosis was found in a group, selected at random, of 150 non-scurbitic subjects of the same age and sex. In the authors' view the evidence suggests that chronic deficiency of ascorbic acid, often unrecognized, may be responsible for osteoporosis in the Bantu.

Joseph Parness.


Few cases of Reiter's syndrome in females have been reported. In this paper three such cases are described. The first patient, aged 41, had acute polyarthritis and bilateral conjunctivitis, lasting 2 months. There was gradual improvement with exercise treatment in bed, but 6 months after discharge from hospital, there was a relapse, which was associated with a vulvo-vaginitis. In the second patient, aged 34, the polyarthritis and conjunctivitis developed about 3 weeks after an attack of acute epidemic diarrhoea. Slight vulvitis was present. The third patient, aged 55, had a yellow vaginal discharge, acute polyarthritis, and photophobia without definite conjunctivitis. In all three cases the erythrocyte sedimentation rate was raised, but the results of other investigations were negative. Urethritis was present in the first case only, and the author suggests that vulvo-vaginitis should be accepted as a cardinal feature of the syndrome.

K. C. Robinson.


A study of gastro-intestinal disturbances occurring in 100 cases of "rheumatism" [rheumatoid arthritis] in 23 men and 77 women, mostly under 40, is reported. During the active period of the disease there were various dyspeptic symptoms, the most common being lack of appetite. Hypochlorhydria was frequently present. Functional disturbances of the pancreas were slight and usually disappeared when adequate antirheumatic therapy was given. Investigations of liver function indicated that its antitoxic and prothrombin-forming activities were more frequently affected than those functions concerned with carbohydrate metabolism.

A. Orley.


Over a period of 3½ years the erythrocyte sedimentation rate (E.S.R.) was determined by Westergren's method in some 900 new cases of rheumatism at Hammersmith Hospital (Postgraduate Medical School of London). In 51 of these there was an inexplicably high E.S.R. of more than 29 mm. in one hour. Of these 51 patients, 45 were re-examined, the E.S.R. being determined again within one month of the first visit. It was found that in fourteen of the patients the E.S.R. had returned to normal. Of the 31 in whom the E.S.R. remained high, eight developed typical rheumatoid arthritis, six were probably suffering from this disease, and in six other disease processes were diagnosed. In eleven instances
no cause could be found for the raised E.S.R., and the general health of these patients has continued good.

Discussing these findings, the authors emphasize that a raised E.S.R. should call for a careful assessment and investigation of the patient, although it is not necessarily associated with a bad prognosis, particularly in older patients.

A. W. H. Foxell.


Gout


Following reports of the development of clinical gout in patients receiving chemotherapy for tuberculosis the authors, working at Albany Medical College, Albany, New York, have further investigated the effect of pyrazinamide and PAS on uric acid levels in the blood and urine. The subjects comprised ambulatory male patients [number not stated] aged from 23 to 68 years from the general medical wards and five tuberculous patients receiving long-term therapy with pyrazinamide and isoniazid; patients receiving uricosuric agents or showing evidence of renal or hepatic disease were excluded from the study. Pyrazinamide 3 g., isoniazid 300 mg., PAS 12 g., and probenecid 2 g., were given daily in various combinations, at first for 7-day periods and subsequently in some cases for 14 days. Samples of blood for serum uric acid estimations were obtained 16 hours after the last dose of the drugs, and the accuracy of the 24-hour urine volumes (since the patients were ambulatory) was checked by creatinine estimations. The method of Dubbs and others was used for the determination of uric acid levels and that of Alvine and Miller for inulin clearance.

Pyrazinamide caused a fall in the urinary output of uric acid by the second day and a rise in the serum uric acid level, which reached a peak between the 5th and 7th days. This was unaffected when isoniazid was then given in addition, but when both drugs were discontinued the serum uric acid level fell and the urinary output rose. Inulin clearance results showed no alteration in the glomerular filtration rate during or after therapy. When pyrazinamide and isoniazid were given together from the outset a similar result was obtained; there was no change when isoniazid alone was withdrawn, but a fall in the serum uric acid level and a rise in urinary uric acid content occurred when pyrazinamide was withdrawn.

In one of the three subjects receiving pyrazinamide in addition to PAS and isoniazid, a similar result was recorded, but in the other two the rise in the serum uric acid level and the fall in urinary uric acid output was less, and marked changes did not occur until 7 days after withdrawal of the PAS. Four patients received pyrazinamide and isoniazid for a long period and three were given this combination for one week, all being then given PAS; in three (two receiving long-term and one short-term treatment) no effect was noted, while in the other four there was a fall in serum uric acid level and a rise in urinary output. Probenecid, which was given with pyrazinamide in four cases, appeared to suppress the hyperuricaemia in two of them and in the other two to delay it; in all four there was a rapid rise in serum uric acid level when probenecid was stopped while the administration of pyrazinamide was continued. Lastly, of four tuberculous patients receiving long-term therapy with pyrazinamide, three showed no change on receiving probenecid and one showed some response, this being the subject who had previously responded to PAS. In one case ACTH (corticotrophin) was given after treatment with pyrazinamide for 8 days and this caused a marked urinary excretion of uric acid and fall in the serum uric acid level.

The authors conclude that the rise in serum uric acid concentration following administration of pyrazinamide is due to decreased excretion of uric acid in the urine, which in turn is presumably the result of increased tubular reabsorption. The hyperuricaemia was unaffected by isoniazid, reduced in some cases by PAS and by probenecid, and completely reversed in the one patient treated with ACTH.

B. M. ANSELL.


At the University of California, Los Angeles, the authors have investigated the reported hyperuricaemic effects of pyrazinamide in 46 patients suffering from pulmonary tuberculosis (but with normal renal and hepatic...
function) who were receiving various combinations of the following drugs: streptomycin 1 g. intramuscularly twice weekly, isoniazid 300 mg. daily, PAS 12 g. daily, and pyrazinamide 1·5 or 3 g. daily. Throughout the study the patients were given their usual diet. A group of ten similar patients not receiving pyrazinamide served as controls. Serum uric acid determinations were performed by a modification of Koch's method.

In the 46 patients who were receiving pyrazinamide, the serum uric acid level was persistently between 6·2 and 9·7 mg. per 100 ml. compared with a level of less than 5·5 mg. per 100 ml. in the controls. This occurred whether the daily dose of pyrazinamide was 1·5 or 3 g. Further, of eleven new patients treated with pyrazinamide and isoniazid, all showed a rise in serum uric acid level whichever dosage of pyrazinamide was employed, and a further eight patients receiving streptomycin and isoniazid all showed a rise in serum uric acid level 48 hours after the addition of 3 g. pyrazinamide daily to the regimen. In five treated with isoniazid and PAS, the addition of pyrazinamide caused only slight changes in the serum uric acid level at 48 hours, but a definite increase after 9 days. One patient under treatment with streptomycin and isoniazid and who was also receiving sodium salicylate for arthritis did not develop hyperuricaemia on the addition of pyrazinamide, nor did two patients given salicylates before and during the administration of 3 g. pyrazinamide daily.

The authors conclude that pyrazinamide in a dosage of 1·5 or 3 g. daily causes a persistent hyperuricaemia which is delayed but not prevented by the administration of PAS and is unaffected by other antituberculous drugs. The hyperuricaemia is, however, prevented by salicylates. It is noted that none of the patients studied complained of joint pains, nor were any attacks of gout observed.

B. M. Ansell.


The authors, writing from the University of Chile, Santiago, review the anatomy and physiology of capillary arteriovenous shunts in the peripheral circulation in man, as described by Chambers and Zweifach, Vogler, and others, and discuss the theory of Wood (Brit. med. J., 1950, 1, 562) that these small anastomoses are implicated in the production of the pain, heat, and redness of the para-articular skin in acute gout. In the normal leg the amplitude of pulsation recorded by an oscillometer decreases with the distance from the trunk. In the leg affected by acute gout, however, the authors have confirmed the findings of Wolfson and Robinson (J. Lab. clin. Med., 1951, 38, 951) that pulsation in the inferior tibial region is greater than that in the femoral region.

"Hydergine" (a preparation of ergot alkaloids) in a dose of 2 ml. was injected into the femoral or brachial artery of the affected limb in four cases of acute gouty arthritis, smaller doses being subsequently given, first by intramuscular injection and then by mouth, for periods up to 15 days. In a further four cases the initial intra-arterial injection was omitted, but the treatment was otherwise the same. An improvement was observed in the affected joint within 5 minutes of the intra-arterial injection of hydergine, the skin becoming pale and the part less painful, while the abnormal oscillometer gradient was reversed. The peri-arterial injection of procaine did not produce the same effect. In the second group of cases the action of hydergine was less spectacular, but the treatment was considered to produce a similar degree of improvement [there were no controls] in about 2 days, after which it was continued for maintenance purposes. In neither group were the symptoms completely abolished by hydergine therapy.

Allan St. J. Dixon.


There is still confusion as to the role of the kidney in the pathogenesis of gout. The original concept suggested by Garrod (Med.-chir. Trans., 1848, 31, 83) of a specific renal lesion was supported by other early studies of urate clearance. However, subsequent workers have found an occasional patient with an abnormally high excretion of urate.

The present authors, working at Mount Sinai Hospital, New York, have therefore undertaken extensive investigations of the renal function in 300 patients suffering from primary gout in various phases of the disease; the ages of the patients ranged from 25 to 79 years and all but nine were male.

As judged by the results of routine urine analysis, the urine concentration test, phenolsulphthalein excretion, and the serum non-protein nitrogen level, 65 patients, mostly in the older age group, had overt renal damage and many of these also showed evidence of vascular disease elsewhere. In addition, 27 patients had nephrolithiasis and sixteen had hypertension without evidence of impaired renal function. In all cases 24-hour collections of urine were made after the patient had been receiving a low-purine diet, and the value for urate excretion was based on the mean result of analyses of at least two 24-hour collections. Inulin and urate clearances were measured in 150 gouty and twelve non-gouty subjects, paraaminohippurate (PAH) clearance in 110 of the gouty subjects concurrently, and in fourteen cases TmPAH was also measured. In addition, the one-hour clearance of urate and creatinine was observed in 64 gouty males, 49 healthy males, and 52 healthy females. The determinations of the urate level in the blood and urine were made by a modification of the colorimetric method of Buchanan and others, incorporating the use of uricase.

There were wide variations in inulin clearance. Comparison of the distribution of the results with those for non-gouty subjects showed a close general correspondence, particularly in the older patients, in whom a reduction in inulin clearance was probably related to degenerative changes in the renal vasculature associated with ageing. The PAH clearance studies revealed a
moderate but significant reduction in effective renal plasma flow in the patients with gout, the exact significance of which is not obvious. The four patients in whom the lowest Tm values were obtained all had presumptive renal vascular disease. There was a general increase in the filtered urate load, which was more pronounced in those with serum urate levels above 8 mg. per 100 ml. When the filtered urate load was within the low normal range it was associated with advanced age or systemic vascular disease. The rate of urinary urate excretion varied considerably in the 150 gouty subjects studied, being greater than the mean range in thirty cases, in which also the mean plasma urate level was higher than in the remainder; however, the majority of the results fell within the normal range, despite some evidence of renal impairment. Tubular reabsorption of urate in the 150 gouty subjects showed wide variations, its magnitude being a linear function of the filtered urate load; there was no difference in the range from that in the controls. The available clearance data do not suggest a tubular excretion of urate, but rather that the filtered urate load is normally largely reabsorbed and that the fraction excreted in the urine is derived from tubular secretion. Urate clearance was usually within the lower limit of normal variation.

The 24-hour urinary urate excretion showed a very much wider range than in normal subjects, and was excessive in 87 cases. The 54 patients in whom excess urate excretion was particularly marked were free from renal damage, belonged to the relatively young age groups, and tended to have a higher serum uric acid level and a lower incidence of visible tophi. At the other end of the scale a low urate output was usually associated with renal impairment. In a few cases it was possible to demonstrate that an observed progressive decrease in urate excretion was the result of deterioration in renal function.

Thus in most gouty subjects the authors demonstrated normal discrete renal functions, but with advancing age and longer duration of the disease the glomerular filtration rate declined and there was also some deterioration in tubular function, these changes being followed by renal retention of urate. They were unable, however, to demonstrate a primary defect in tubular function causing enhanced tubular reabsorption or deficient tubular secretion of urate, and therefore conclude that there is no primary renal defect in gout. They suggest that the hyperuricaemia is an expression of an inborn error of metabolism profoundly affecting some aspect of intermediary purine metabolism and leading to overproduction of urate.

B. M. Ansell.


As a remedy for gout colchicine has been in use since the 5th century, but its mode of action is still little understood. In studies of this drug at the Faculty of Medicine of Strasbourg, the author has been impressed by its anti-allergic properties when given intravenously.

In some ways it behaves like adrenaline; thus a dose of 3 mg. may raise the arterial blood pressure by 10 to 20 mm. Hg in normal individuals, and in those who are hypotensive from shock by as much as 40 mm. Hg. The drug also potentiates the action of adrenaline. The above dose will produce a fall in the number of circulating eosinophil granulocytes to the level obtained by the intravenous infusion of 1 mg. of adrenaline (25 mg. ACTH will result in a much greater fall). When the intravenous infusion of colchicine (3 mg.) is repeated several times at intervals of 24 hours there is a rise in the urinary excretion of dehydroandrosterone and 17-ketosteroids.

An acute attack of gout is characterized by intense dilatation of the small vessels and by interstitial oedema, comparable to the conditions seen in serum arthritis. Pain is particularly severe in areas where the surrounding tissues are dense, while relief is felt the moment there is diminution in the swelling of the interstitial tissue. In therapeutic doses colchicine causes vasoconstriction at skin level—an observation which can be confirmed in urticarial oedema. It also reduces capillary permeability. When given intravenously colchicine causes blanching of the affected tissues within 5 to 10 minutes, thus producing an adrenaline-like effect. The second stage of its action may be delayed for several hours and corresponds to the time required for the drug to permeate the nervous system; its ACTH-like effect appears to belong to this second stage.

D. Preiskel.


Pararheumatic (Collagen) Diseases


The results obtained over a 3-year period with the L.E.-cell test in patients suffering from lupus erythematosus and in patients with other diseases are reported in this paper from the Postgraduate Medical School of London. Two techniques were used:

(1) Defibrinated blood was incubated for 2½ hours at 37° C., then centrifuged, smears being obtained from the leucocyte layer;
(2) normal leucocytes were suspended in the patient's serum, incubated for 2½ hours at 37° C., and centrifuged, smears being then made from the leucocyte button.

In eighteen out of nineteen patients with systemic lupus erythematosus the results of the L.E.-cell test were positive. No relationship was found between the intensity of L.E.-cell production and the severity of the disease,
but it was confirmed that adequate hormone treatment led to a marked reduction in the number of L.E. cells produced. L.E.-cell tests were carried out on blood from 495 patients with diseases other than systemic lupus erythematosus, including nine with cutaneous lupus erythematosus, 106 with rheumatoid arthritis, twenty suffering from drug reactions, 44 from cirrhosis, and a number with many other diseases. A positive result was obtained in one patient only, a young woman with portal cirrhosis.

The authors conclude that the L.E.-cell phenomenon is specific for systemic lupus erythematosus, "but that rare false-positive reactions are seen in cases of hydralazine sensitivity and cirrhosis". E. G. Rees.


In the opinion of the authors the histological changes occurring in muscle in dermatomyositis and the collagen diseases have not been studied in sufficient detail. As a result of studies carried out at the Hôpital Saint-André, Bordeaux, they now report the following findings. In dermatomyositis the initial change is oedema both of the muscle fibres and of the interstitial tissue. In the muscle parenchyma a number of different changes may occur side by side, or may be present in one area and absent in a neighbouring one. These changes consist in loss of transverse striations, granular degeneration of whole fibres or parts of fibres, and the appearance of waxy amorphous masses; vacuoles may be seen in some of the fibres, and the cell nuclei increase in numbers without the occurrence of mitotic figures. The interstitial changes are equally varied; here there may be infiltration of histiocytes and lymphocytes, and plasma cells and eosinophils are sometimes also present; the amount of fibrosis is variable. The vessels show no major alterations.

In early lesions the changes are found only in the parenchyma, but in later lesions they are interstitial as well as parenchymatous, and sheets of lymphorrhage are present. In scleroderma the principal changes are interstitial, with dense infiltrates of lymphocytes and histiocytes followed by fibrosis of the collagen. In acute disseminated lupus erythematosus the oedema is relatively mild, the blood vessels are dilated, their walls are slightly thickened, and the lymphocytic infiltration is perivascular. In polyarteritis nodosa the vessels show thickened, infiltrated walls, sometimes accompanied by endarteritis and thrombosis and fibrinoid degeneration of the collagen. In this condition the changes in the muscle fibres are only slight. E. Lipman Cohen.


This paper gives a general review of the histological findings in fifteen cases of disseminated lupus erythematosus studied at the University Institute of Pathological Anatomy, Copenhagen. It is the authors' thesis that this disease is probably an immunological disorder characterized by material giving a positive periodic-acid-Schiff reaction and therefore containing carbohydrate which has been produced in reticulo-endothelial cells. They point out that the haematoxyphil bodies typical of the disease give the same reaction, as also do the hyaline thrombi and "wire-loop" lesions of the renal glomeruli and material in the characteristic granulomata and nodular necrotic lesions of the lung, serous membranes, and lymph nodes.

They dissent from Klemperer's hypothesis that an alteration of nucleoprotein is the primary change, and from the idea that the fibrinoid deposits are derived from the circulating blood.

If it be assumed, as seems most likely, that disseminated lupus erythematosus is an immunological disorder characterized by the presence of a circulating antibody directed against nucleoprotein it follows that this antibody, being a $\gamma$ globulin, would contain appreciable amounts of carbohydrate which would give a positive periodic-acid-Schiff reaction, and its combination with nucleoprotein and deposition in the tissues along with fibrin would account for many of the features of the disease. In the abstractor's opinion, therefore, the difficulties which the authors find in accepting such an assumption are more apparent than real, and are due to a preoccupation with isolated facets of the disease.

M. C. Berenbaum.


The authors report from the University of Pittsburgh School of Medicine the detailed clinico-pathological investigation of nine patients with systemic scleroderma, of whom seven died as a result of malignant hypertension and rapid renal failure; of the other two patients one had only mild renal dysfunction and in the other extensive renal lesions were discovered only post mortem. In the seven fatal cases the termination of the illness was characterized by the development of headaches, failing vision, and hypertension. In some cases uraemic coma and convulsions supervened immediately before death, which occurred within a few months of the clinical recognition of renal involvement. Only three of the patients had not received steroid therapy during the course of their illness. Histological examination of the kidneys in six cases revealed three striking pathological changes, consisting in

1. intimal thickening of small interlobular arteries and arterioles.
2. fibrinoid necrosis of afferent arterioles and glomerular loops,
3. multiple cortical infarcts.

Similar changes were found in the viscera.

Reviewing the literature the authors note that renal involvement in systemic sclerosis is by no means rare,
although often there may be no clinical manifestations. The precise role of ACTH and cortisone in the development of these renal lesions is discussed, but neither the literature on the subject nor the authors’ investigations provide a satisfactory conclusion. There is, however, some evidence that the use of hypotensive drugs may initiate renal failure in patients whose hypertension is related to systemic sclerosis. On the other hand it has been held that the renal changes may result from the hypertension itself—whatever its cause in systemic sclerosis—but the authors describe one case in a patient with typical renal changes who remained normotensive throughout the disease. They conclude that renal involvement in systemic sclerosis occurs more frequently than has been supposed, that this represents true involvement of the kidney in this disease, and that the ensuing malignant hypertension, although it adds its particular signature to the renal pathology, does not account for all the changes that may be demonstrated.

J. N. Harris-Jones.


It is well recognized that there is an association between systemic lupus erythematosus (S.L.E.) and hypergammaglobulinaemia. There is evidence of an inherited tendency in both discoid lupus erythematosus and agammaglobulinaemia. The author of this paper from Malmö General Hospital, Sweden, attempts to demonstrate an inherited tendency for the association of S.L.E. with hypergammaglobulinaemia. He describes four siblings (sisters) out of a family of 14 in which hypergammaglobulinaemia was “strikingly frequent”. In two of the siblings a diagnosis of systemic lupus erythematosus was established beyond doubt, and both died from this disease; in one of these, severe relapses occurred following administration of phenylbutazone. S.L.E. was also diagnosed in a third sister (a twin), although the presence of L.E. cells was not demonstrated. The fourth sister, who had received treatment for gonorrhoea, complained of arthralgia; in this patient the erythrocyte sedimentation rate was raised and the results of flocculation tests were abnormal. All four sisters had hypergammaglobulinaemia. Of the fourteen siblings, six were considered to show a moderate increase in the gammaglobulin fraction—0.94 to 1.17 g. per 100 ml.; in four others it ranged from 1.37 to 1.46 g. per 100 ml.; and in one a level of 3.78 g. per 100 ml. was recorded.

In this sibship, therefore, the author found three cases of S.L.E. and a significantly high incidence of hypergammaglobulinaemia in the remainder. It is suggested that the inherited mechanism is a tendency towards overproduction of antibodies and gamma globulin. Once hypergammaglobulinaemia is established unfavourable antigens may provoke S.L.E. In support of this theory the author cites the sibling who, known to have marked hypergammaglobulinaemia, developed classical S.L.E. following treatment with phenylbutazone.

J. N. Harris-Jones.


This paper summarizes a report to the Collagen Diseases and Hypersensitivity Panel of the Medical Research Council in which 111 histologically proven cases of polyarteritis nodosa occurring during the period 1946-53 in nine teaching centres in Great Britain are surveyed. The author suggests the presence or absence of pulmonary involvement as a useful basis of classification. In 32 of the cases involvement of the lungs was diagnosed on pathological evidence or from the presence of other features considered to be characteristic of pulmonary polyarteritis, in 66 involvement of the lungs was regarded as absent, in six such involvement was doubtful, and the remaining seven cases presented features differing markedly from those of the remainder. (These last two groups are mentioned only briefly.) There were 66 patients (41 males and 25 females) in the group without lung involvement. At the time of onset thirty (45 per cent.) had chronic respiratory infection or had recently had an acute upper respiratory infection, and six (9 per cent.) had active or quiescent chronic polyarthritis. Clinical manifestations were varied. Gastro-intestinal pain or haemorrhage occurred in 46 cases (70 per cent.) and muscular pain and tenderness were early and frequent manifestations. Focal indurated nodules, ulcers, or papules of the skin were seen in eighteen cases (27 per cent.) in addition to purpura and other skin lesions. There was evidence of peripheral neuritis in 24 cases (36 per cent.). Arthritis, either acute and transient or of a rheumatoid type, occurred in eighteen cases (27 per cent.). Splenomegaly was present in eight cases. Anaemia, leucocytosis, and a slight to moderate eosinophilia were common. There was evidence of coronary involvement in 32 cases (48 per cent.), but pulmonary manifestations in this group were all attributable to infection or cardiac failure. Renal involvement occurred at some stage in 52 cases (79 per cent.), renal polyarteritis being found at necropsy in 39 out of 54 cases and a specific form of glomerulitis in sixteen. Hypertension did not develop in the acute stage of the latter type of renal involvement, but the three patients who survived this stage developed progressive hypertension and uraemia and died within a year. The renal lesions were the primary cause of death in 65 per cent. of the 55 fatal cases, most of the other deaths being due to coronary or gastro-intestinal polyarteritis. Of the 54 patients not treated with cortisone or corticotrophin, 51 died within 6 months, but in many of these cases the diagnosis was first made at necropsy. There were sixteen males and sixteen females in the group of patients with lung involvement. Clinically, the main features of pulmonary polyarteritis were those of asthma (with no family history), chronic bronchitis, or pneumonia. In eight cases there was a long previous history of respiratory infection and in six one of rheumatic fever. Haemolytic streptococci were isolated from the sputum in 23 per cent. of the cases in which it was examined. Eosinophilia was observed in a high proportion of cases, frequently reaching 5,000 or more per c.mm. At necropsy gross pulmonary damage was the...
rule, either from nodular or caseous lesions or from haemorrhagic pneumonia, infarction, or fibrosis. Microscopical examination showed pulmonary polyarteritis and characteristic necrotizing or granulomatous lesions. The incidence of polyarteritis in other organs and the accompanying clinical manifestations was broadly similar to that in the first group. The mean total survival time was longer in cases with pulmonary involvement than in those without, but the period of survival from the onset of systemic polyarteritis was shorter; this probably accounted for the less frequent finding of hypertension in the former type of case. Of the 32 patients with involvement of the lungs, eight received cortisone or corticotrophin, but only one (treated with cortisone) survived. Pulmonary lesions accounted for 42 per cent. of the deaths and renal lesions for 26 per cent.

The author considers that a preceding chronic or acute respiratory infection, especially with the haemolytic streptococcus, is a factor in the aetiology of polyarteritis nodosa, but that the treatment of such infections cannot be incriminated. The association with rheumatic fever and rheumatoid arthritis is also stressed.

J. Warwick Buckler.


Non-Articular Rheumatism


General Pathology


A modification of the Rose-Waaler haemagglutination test (Boisvert and others, Yale J. Biol. Med., 1956, 28, 622) was applied at Yale University School of Medicine to specimens of serum and synovial fluid taken simultaneously from ten patients with rheumatoid arthritis and six with other types of arthritis. In five of the latter cases, the possibility of rheumatoid arthritis had not been finally excluded. The effects of incubating both serum and synovial fluid for one hour at 37° C. with various concentrations of hyaluronidase were studied. This procedure increased the agglutination titre in the case of certain specimens of synovial fluid, the optimum concentration being found to be between 150 and 250 turbidity reducing units per 0.3 ml. fluid in an acetate buffer of pH 6.0, but had no effect on the titre of serum. Similar tests were carried out with $\beta$ glucuronidase at pH 6.5, but this enzyme had no significant effect.

In three cases of rheumatoid arthritis and one of possible rheumatoid arthritis, tests on serum gave positive
and on untreated synovial fluid negative results; in two cases of rheumatoid arthritis, both serum and synovial fluid gave positive results; and in the remaining ten cases both gave negative results. After hyaluronidase treatment six of the specimens of synovial fluid which had previously given negative results gave a positive result and three others a borderline result. In two of the former and all the latter cases the serum had given a negative response, two of them being cases in which the clinical diagnosis had been doubtful. In a further series of tests synovial fluid from nine subjects without either rheumatoid arthritis or the possibility of such a diagnosis gave negative agglutination responses and only one of these became positive after hyaluronidase treatment.

The authors do not consider that the physical change in viscosity resulting from the incubation of synovial fluid with hyaluronidase is itself responsible for the unmasking effect on the haemagglutination reaction, since preliminary experiments have indicated that treatment with hyaluronidase can convert an atypical haemagglutination pattern into a typically positive one even when a high viscosity is artificially maintained with glycerol or methylcellulose.

E. G. L. Bywaters.


It is not generally realized that the erythrocyte sedimentation rate (E.S.R.) may increase twofold with variations in room temperature normally found in wards and laboratories in Great Britain and other temperate climates. The E.S.R. was determined by the method of Westergren on 143 occasions in 33 patients at St. Stephen’s Hospital, London. The results obtained over a temperature range of 12-8°C in fifteen patients are given in a table. It was found that the Westergren E.S.R. was affected "to an important degree" by normal variations in room temperature and to a greater extent and over a greater range than the E.S.R. as measured by Wintrobe’s method.

A nomogram for correction of Westergren’s method is given.

A. W. H. Foxell.


The original methods for the demonstration of a "rheumatoid factor" in the serum of patients with rheumatoid arthritis by means of an agglutination reaction were those set out by Rose and Waaler, using sensitized sheep erythrocytes. Singer and Plotz have since shown that the sheep cells can be replaced by polystyrene globules or latex particles, and Heller that the sensitizing serum can be replaced by Cohn’s Fraction II of human serum. (Rehins and others have shown that γ globulin from the serum of numerous animal species will react with the “rheumatoid factor” and give equivalent results.)

In the present paper from the British Columbia Medical Research Institute, Vancouver, it is stated that the “rheumatoid factor” will react in a similar way with latex particles treated with chondroitin sulphate, hyaluronic acid, or heparin. Sera from 312 patients, including 71 with rheumatoid arthritis, were examined, the standard latex fixation test being performed simultaneously with latex particles treated with Fraction II, with untreated latex particles, and with latex particles treated with each of the three polysaccharide substances. The results obtained with each method are discussed at some length and it is concluded that the specificity of the tests with the polysaccharides is comparable to that of the standard latex fixation test, though the possibility is admitted that small quantities of active globulin are present as a contaminant in the various polysaccharide preparations. One important implication of these findings is the possibility that an auto-immune reaction between these polysaccharide components of joint tissues and the “rheumatoid factor” in the serum may supply the basis of the chronic inflammatory process of rheumatoid arthritis.

**Harry Coke.**


From Queens University, Kingston, Ontario, the author reports a morphological and histochemical study of the subcutaneous nodules of rheumatoid arthritis, sections from both paraffin-imbedded and freeze-dried material being examined. The usual methods of staining showed some central necrotic material enclosed by layers of fibrinoid, fibrin, and surrounding cells in the familiar pallisade formation. The material described as fibrinoid showed a positive periodic-acid-Schiff (PA-S) reaction but no metachromasia. It gave positive reactions to histochemical tests for tyrosine, tryptophan, cysteine, and cystine. Treatment with hyaluronidase reduced or abolished staining by alcian-blue, but had no effect on the PA-S reaction. Collagenase had no effect, but both trypsin and fibrinolysin interfered with the staining of fibrinoid.

On morphological grounds the author considers that fibrinoid is in fact related to fibrin, since it seemed to exude from blood vessels and to occur near them in recently formed nodules. He also cites as evidence for this view that Mallory’s phosphotungstic-acid-haematoxylin stain colours both fibrin and fibrinoid blue. He suggests that the presence of the amino-acids indicates fibrin rather than one of the products of connective tissue, and concludes that these findings afford indirect evidence which suggests that the origin of fibrinoid is from fibrin.

G. Loewi.


An increase in the plasma concentration of acid mucopolysaccharides in cases of rheumatoid arthritis having
been reported by Badin and others (J. clin. Invest., 1955, 34, 1317), the present author, working at the Brookhaven National Laboratory, Upton, New York, has estimated the output of acid mucopolysaccharides in 24-hr specimens of urine from such patients by precipitation with cetyltrimethylammonium bromide and determination of the glucuronic acid content of the precipitate (di Ferrante and Rich, J. Lab. clin. Med., 1956, 48, 491). In a study of eight patients with active untreated rheumatoid arthritis a significant increase above the average normal value was demonstrated. In five of these cases treatment with salicylates (about 4 to 5 g. a day) resulted in a significant fall in mucopolysaccharide excretion.

By treating 20 litres of pooled urine from patients with rheumatoid arthritis a sufficient quantity of mucopolysaccharide was isolated for more detailed analysis by chromatography and electrophoresis and comparison with material derived from healthy subjects. Evidence is adduced in support of the hypothesis that the acid mucopolysaccharides in urine from normal individuals and patients with rheumatoid arthritis are derived from similar substances in the plasma and consist of a mixture of chondroitin sulphate and hyaluronate. Harry Coke.


The agglutination of sensitized sheep's erythrocytes by the serum from patients with rheumatoid arthritis has been attributed to the presence of a specific "rheumatoid factor", and in this paper from the Karolinska Hospital and Medical Nobel Institute, Stockholm, the authors outline the series of investigations which have led to the isolation of a refined complex which can be said to constitute this factor. The factor was first separated from other similar complexes causing agglutination by the cold precipitation technique and subjected to electrophoretic analysis, which showed it to be a fast-moving \( \gamma \) globulin of a nearly homogeneous nature. By ultracentrifugation with a separation cell the cold precipitate was then divided into a top fraction, containing chiefly globulins with a sedimentation constant of 6 to 7 S, which had no haemagglutinating activity, and an active bottom fraction containing a large amount of globulins with a sedimentation constant of 19 to 22 S. The haemagglutinating rheumatoid factor was thus shown to be bound to a fraction containing macroglobulins. Repeated serial ultracentrifugation failed to further the purification of the factor, which was finally achieved chromatographically by the use of the cation exchanger carboxymethylcellulose. The cold precipitate was dissolved in saline and applied to a column of carboxymethylcellulose, the adsorbed proteins being eluted with a continuously increasing pH gradient. One fraction was isolated that gave a stronger haemagglutination reaction than the rest and on analytical ultracentrifugation showed only a single peak, having a sedimentation constant of 18-7 S. The concentration of this component was found to be almost proportional to the haemagglutinating power of the active fractions. The authors are therefore able to state that the "rheumatoid factor" is a macroglobulin with a sedimentation constant of 18-7 S which behaves electrophoretically as a fast-moving \( \gamma \) globulin.

[Further analysis of this complex will be awaited with much interest.] Harry Coke.


The structure of the renal glomeruli was examined by the light and electron microscopes in biopsy material from 76 children suffering from nephrosis, glomerulonephritis, and lupus erythematosus. It is pointed out that the normal glomerulus has three components—the endothelium, basement membrane, and epithelium. In the patients with nephrosis there was a loss of the characteristic organization of the epithelial cytoplasm into foot processes. (This was especially marked, and appeared to be the only change, in cases of "pure" nephrosis.) The capillary loop surfaces were covered by broad masses of epithelial cytoplasm. There was also an increase in the number of vacuoles. Swollen endothelium with numerous intracytoplasmic vesicles and some changes in the basement membrane were observed. The glomeruli in glomerulonephritis showed mainly proliferative changes of the endothelium and basement membrane. In the acute stage of the disease the number of endothelial cells was increased; in addition cytoplasmic swelling of both endothelium and epithelium and thickening of the basement membrane with accumulations of "basement-membrane like" material were seen. In the subacute and chronic stages the glomeruli consisted of tangled masses of cells with few open blood channels. The most characteristic finding in lupus erythematosus was a thickening of the basement membrane with some endothelial proliferation. This could be seen before any sign of the "wire-loop" by light microscopy; similarly the changes in nephrosis were seen by the electron microscope before they were detected by the conventional microscope.

In the later stages of these three disease conditions no distinction between them was possible by the electron microscope, the appearances in all three being very similar. As expected, there was a considerable overlap in the appearances in many of the cases. G. Loewi.

Objective Evaluation of Patients with Rheumatic Diseases.


A comparative study of the value of various laboratory procedures in the estimation of the severity and duration of disease activity in rheumatic fever was undertaken at the Veterans Administration Hospital and Oklahoma School of Medicine, Oklahoma City. The authors
determined the serum concentrations of glycoprotein, seromucoid (using tryptophan estimation), and C-reactive protein, and the serum antistreptolysin-O titre, comparing the values obtained with the erythrocyte sedimentation rate (E.S.R.) [method not stated] and the clinical findings. There was some overlapping between patients with "active" and those with "inactive" disease with all these tests, but each one (with the exception of the antistreptolysin-O titre) appeared to be measuring a similar type of change although the changes took place at different rates.

The most rapid response to changes in disease activity was obtained with the C-reactive protein test, the results of which became negative very quickly after clinical disease activity had subsided. The E.S.R. returned to normal more slowly than did the other values; it was raised in thirteen out of eighteen cases of inactive and in fourteen out of sixteen cases of active disease. The serum glycoprotein level, estimated as milligrams of bound hexasyl per 100 ml. serum or as a percentage of the total serum proteins, was raised in all eighteen cases of active disease, as was the seromucoid level. The former was raised in nine out of the 21 inactive cases and the latter in four out of sixteen such cases. The antistreptolysin-O titre showed no clear relationship with inflammatory activity.

E. G. L. Bywaters.


For the past 5 years the erythrocyte sedimentation rate (E.S.R.) of all in-patients at the Special Unit for Juvenile Rheumatism, Canadian Red Cross Memorial Hospital, Taplow, has been measured every week by both the Westergren and the Wintrobe methods, the total number of duplicate readings thus obtained being approximately 19,000. In order to study the incidence and causes of the anomalously low results sometimes obtained by the Wintrobe method in the presence of a very active disease process the authors have analysed the 2,540 pairs of readings from 100 patients selected at random. This group was mainly composed of children and young adults, of whom forty had rheumatoid arthritis, 47 rheumatic fever or chorea, and the remainder other forms of collagen disease. The results were regarded as discordant if the Wintrobe E.S.R. was less than 20 mm. at a time when the Westergren rate was 50 mm. or more in one hour. In such cases the Westergren rate gave without exception the more accurate reflection of the clinical state. Anomalous readings were obtained by the Wintrobe method on at least one occasion in 26 out of the 100 cases and constituted 4-6 per cent. of the 2,540 readings. On 23 per cent. of the 498 occasions on which the Westergren reading was over 50 mm. in one hour the results were discordant, and in this group of cases the mean packed cell volume (P.C.V.) was 40-6 per cent.; in the remaining 77 per cent. of cases the P.C.V. was 36-5 per cent., the difference being highly significant.

Experiments were then carried out to determine how far the plasma viscosity, the P.C.V., and the internal diameter of the sedimentation tube were concerned in the causation of anomalous results by the Wintrobe method. Plasma viscosity was measured in a modified Ostwald capillary viscosimeter and expressed in terms of its relation to the viscosity of distilled water as indicated by its rate of flow at 37°C. It was found that as the relative plasma viscosity increased beyond 1·8 the mean Westergren reading rose steadily, whereas the Wintrobe reading increased more slowly to a maximum at a viscosity of 2·1 and there after fell again to the level attained at a viscosity of 1·9 to 2. The effect of increasing plasma viscosity on the Wintrobe reading was essentially the same whatever the P.C.V. of the blood. In the lower ranges of viscosity values the Wintrobe readings for blood with a P.C.V. below 39 per cent. were closer to the Westergren readings than those for blood with a higher P.C.V., but there was always a fall in the Wintrobe rate when the plasma viscosity rose above 2·1 or 2·2. The Westergren readings at different levels of viscosity also tended to be somewhat higher with blood of low P.C.V., but remained directly related to the plasma viscosity at all P.C.V. levels. When the P.C.V. was below 40 per cent. the results obtained at different levels of plasma viscosity with a modified Wintrobe tube of 4·5 mm. internal diameter were much the same as those obtained with the standard tube of 2·5 mm. internal diameter. When the P.C.V. was above that level, however, the larger tube gave results more closely resembling the Westergren readings, though the E.S.R. still tended to fall off at the higher levels of plasma viscosity.

The authors conclude that the discrepancy between the results obtained by the two methods is due to the additive effect on the Wintrobe E.S.R. of a high plasma viscosity and the inadequate bore of the standard Wintrobe tube, the discrepancy being more marked when the P.C.V. is over 40 per cent.

R. F. Jennison.


In 1926 Epstein introduced the method of fractional determination of the erythrocyte sedimentation rate (E.S.R.), in which the rate of sedimentation is recorded every 15 minutes over a period of 90 minutes and the results plotted as a curve. The type of curve obtained enables the observer to distinguish five types of E.S.R.: the normal, the areactive, the hyporeactive, the reactive, and the hyperreactive.

The hyperreactive curve, distinguished by rapid sedimentation during the first 30 minutes followed by slowing of the rate, is characteristic of acute infections in a highly reactive subject, for example, in acute rheumatism or pneumonia. The reactive type, in which the most rapid sedimentation occurs in the second or third quarter of the first hour, is found in acute infections in subjects with usually normal reactivity. The hyporeactive curve, in which the highest rate is at the end of the first hour, occurs in convalescent patients or in acute infections in subjects with lowered reactivity. The areactive curve is...
found in cases of overwhelming infection, or in patients with little or no resistance; in this type the curve is very low and nearly horizontal throughout. In the normal curve, as seen in healthy persons, the rate does not rise above normal levels and successive estimations do not differ by more than 1 to 3 mm. per minute. The author states that it is possible by means of fractional estimation of the E.S.R. to evaluate the stage of the infection and the reactivity of the patient, and the procedure is therefore valuable in prognosis, especially in children.

L. Firman-Edwards.


Clinical Significance of Serum Antistreptolysin-O Levels. [In English.] Hsioh-Teh, C., and Hua-Ch'eng, W. (1958). *Chin. med. J.*, 76, 259. 2 figs, 7 refs.


ACTH, Cortisone, and Other Steroids


Following the observation that a patient with Addison's disease had initially a negative Mantoux reaction at a dilution of 1 in 100 but that this reaction had become positive at a dilution of 1 in 1,000 37 days later while she was receiving a daily maintenance dose of 50 mg. cortisone, the author carried out Mantoux tests on all (24) patients admitted with a variety of disorders to Stoke Mandeville Hospital, Aylesbury, Bucks, who were likely to need corticosteroid therapy and who were Mantoux-negative on admission (at a dilution of 1 in 100 in thirteen cases and of 1 in 1,000 in eleven cases). They comprised fourteen men and ten women ranging in age from 24 to 80 years, the majority being over 60 years old.

In addition to receiving the treatment appropriate to their particular ailment these patients were given either cortisone in doses ranging from 25 to 75 mg. daily or prednisolone 15 to 60 mg. daily. Of the 24 patients, twenty subsequently showed a positive Mantoux reaction, three of them who had previously been negative at a dilution of 1 in 100 becoming positive at 1 in 1,000. In the majority of the cases, the time interval between the two tests was less than 2 weeks. The clinical course of
his disease seemed to have no bearing on the reversion to a Mantoux-positive reaction; thus six of those who reverted showed marked improvement, six showed no change, three deteriorated and subsequently died, and three were not very ill at any time.

A further case, that of a man aged 35 with pneumonia and pleural effusion, is recorded in some detail, in which the Mantoux reaction became positive following recovery of adreno-cortical function which had been depressed during the acute stage of the illness, no steroid drugs having been administered. The suggestion is made that although steroid treatment is able to suppress a positive tuberculin reaction when given in high dosage, it may, when given in lower dosage, actually restore a reaction which has been suppressed by age, infection, or adrenal deficiency.

H. F. Reichenfeld.

Possibility of Utilizing Androgens and Oestrogens in the Biosynthesis of Adrenal Corticosterones. (О возможности использования андрогенов и эстрогенов в биосинтезе коры надпочечников)


In addition to the corticosterones the adrenal cortex synthesizes androgens and, to a certain extent, oestrogens, which in some pathological conditions may be stored in considerable quantities. The corticosterones contain 21 atoms of carbon, the androgens 19, and the oestrogens 18. Convincing evidence has been provided by Hechter and Pinkus of the possibility that cholesterol is convertible into corticosteroids, while the present authors have already shown that dehydroisoandrosterone can serve as substrate in the synthesis of corticosteroids. It is therefore reasonable to expect that other steroids with 19 carbon atoms could be converted into corticosterones with 21.

In experiments designed to explore this possibility guinea-pigs (ten in each experiment) were killed and their adrenal glands removed and placed on ice—one from each animal being used for the test and the other serving as control. Slices of the test glands were then incubated in a medium containing androgens or oestrogens, while control slices were incubated in the same medium without such additions. (The medium consisted of Krebs-Ringer-bicarbonate solution, at a pH of 7.3, excluding calcium chloride, but with the addition of sodium fumarate (0.06 per cent.) and magnesium chloride (0.006 per cent.).) After incubation for 3 hours in an atmosphere of 95 per cent. oxygen and 5 per cent. carbon dioxide at 37° C., the steroids were extracted and estimated by Bush's method. It was found that slices of adrenal gland incubated with androstenedione contained double the amount of hydrocortisone found in the control slices. Testosterone was ineffective as a substrate, but the addition of androsterone to the medium produced an even greater synthesis of hydrocortisone, the test slices containing up to treble the amount present in the controls. Oestrone was as effective as androstenedione and oestradiol rather less so. Incubation with adrenosterone caused no increased production of hydrocortisone, but doubled that of cortisone. From the lower efficacy of oestradiol and testosterone as substrates it is concluded that the presence of the 17-ketosteroid group is of great importance for the transformation of oestrogenic or androgenic steroids into corticosteroids.

L. Firman-Edwards.


From the Mount Sinai Hospital, New York, the authors describe studies designed to demonstrate the effects of ACTH (corticotrophin) and cortisone on the rate of re-epithelization and of the healing of experimentally induced gastric ulcers in dogs.

In the first series of experiments, which were performed on dogs with a Heidenhain pouch, the columnar surface epithelium of the stomach down to the necks of the gastric glands was removed chemically by applying eugenol; mucosal biopsy specimens were taken 2, 4, 6, 8, and 24 hours later, the dogs meanwhile receiving a normal diet and fluid intake. The experimental group had received either ACTH (5 to 10 mg per kg body weight) or cortisone acetate (5, 10, or 15 mg/kg) daily for 3 to 6 days before and on the day of the experiment. Examination of the serial biopsy specimens showed that the administration of ACTH or cortisone did not influence the rate of epithelial replacement, which in both groups of animals was virtually complete in 24 hours.

In the second series of experiments, which were designed to study the deeper processes of healing, portions of the entire thickness of the corpus of the canine stomach, with blood supply intact, were transplanted to the anterior abdominal wall. In this situation, and protected by a metal guard, the gastric mucosa could be inspected frequently in the otherwise intact animal. Circular excision ulcers deep enough to include the muscularis mucosae were then made in the transplants, the diameter of the ulcer being defined by a punch biopsy machine. The healing time of the ulcers was determined to the nearest day, disappearance of the ulcer and reconstitution of the surface epithelial layer being the criteria of healing. The test dogs were similarly treated, but received 5 or 10 mg. ACTH or 2.5, 10, or 20 mg. cortisone acetate suspension daily intramuscularly for 3 days before the production of the ulcer and throughout the period of healing. The mean healing time of these excision ulcers was prolonged by both cortisone and ACTH in the doses employed in this study. In the case of cortisone the delay in wound healing was not directly related to the dosage of the drug. All the ulcers healed eventually, despite the relatively large doses of corticosteroids.

The authors suggest that adrenocortical hormones may increase the process of existing peptic ulceration, apart from any effect they may have in augmenting the gastric secretion of acid and proteolytic enzymes.

T. J. Thomson.

Other General Subjects

This paper describes the experience of the authors in treating 117 patients suffering from rheumatoid arthritis and ankylosing spondylitis who were admitted to the Canadian Arthritis and Rheumatism Society's medical rehabilitation centre at Vancouver. In the centre nursing care was not available, and treatment consisted of medical care and re-training by means of physiotherapy and occupational therapy, and guidance by the almoners.

Of 22 patients suffering from ankylosing spondylitis fourteen came in unable to work, and when the report was written, thirteen were at full-time work, one at intermittent work, and only eight were still unable to work.

Of 39 men suffering from rheumatoid arthritis, 34 were initially unable to work, and only one was working full time. These figures were reversed to the extent that thirteen were got on to full-time work and 21 were still not working.

Of 56 women suffering from rheumatoid arthritis, ten were initially working full time and of the remainder 23 were working part-time and 23 not at all. These figures changed to the extent that 31 returned to full-time work and only twelve remained unable to work.

The authors point out that many of those not yet at work are still salvageable, and that in some cases factors other than the disease prevent their working.

Discussing their results, the authors point out that they are dealing with diseases of an unpredictable course. Many of the patients were dependent, poor personalities, without the will to help themselves. But some of these finally co-operated well after training had started. In spite of such difficulties the work was found to be satisfying and encouraging.

W. Tegner.

Chloroquine in the Management of Hypersensitivity States.
Abstracts

Ann Rheum Dis 1958 17: 342-358
doi: 10.1136/ard.17.3.342

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