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; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section “ACTH, Cortisone, and other Steroids” includes abstracts and titles of articles dealing with steroid research which, although not directly concerned with the rheumatic diseases, may make an important contribution to knowledge of the scope and modus operandi of steroid therapy.

Acute Rheumatism


The inhibitory action of salicylates on hyaluronidase has been attributed to liberation of heparin in the tissues, and favourable results have been reported from the administration of heparin and similar anticoagulants in the treatment of rheumatism. These have been explained as being due to either an anti-exudative effect through osmotic and diffusional regulation, or to an anticoagulant effect diminishing antigen-antibody reactions, an anti-hyaluronidase action, or an anti-anaphylactic action. In this study, carried out at the Institute of Clinical Paediatrics, University of Genoa, three lines of enquiry were pursued:

1. The relative tolerance to heparin of rheumatic and non-rheumatic children;
2. The effect of hyaluronidase on clotting factors in vitro;
3. The relation between hyaluronidase, heparin, and salicylate in regard to intradermal diffusion of coloured substances.

Heparin tolerance of non-rheumatic control patients and a group of fifteen salicylate-treated rheumatic children was estimated by comparing the coagulation times at 10, 30, and 60 min. after intravenous injection of 2,000 units of heparin. The non-rheumatic patients showed an average coagulation time of 37 seconds at 10 min., compared with 30 seconds in the rheumatic group. Since five non-rheumatic and two rheumatic patients had coagulation times of 50 seconds or over at 10 min., this estimation was used as a screening test for heparin treatment.

The effect of hyaluronidase on clotting factors in vitro was then investigated. Samples of blood from ten children free from haematological disease were examined for prothrombin time (in the presence of progressive dilutions of thrombin), for recalcification time, and for antithrombin time, and the effect on these figures of distilled water and hyaluronidase in solutions of 25 and 1-25 units per ml. determined. Prothrombin and recalcification times were prolonged and the antithrombin time little affected. (As these results were similar to those obtained with heparin, the effects of a heparin-hyaluronidase mixture were not investigated.)

Lastly, the relation between hyaluronidase, heparin, and salicylate in regard to intradermal diffusion of coloured substances was investigated, mixtures of fluorescein and distilled water and fluorescein and hyaluronidase being viewed by ultraviolet light through Wood's glass in two groups of subjects—non-rheumatic children injected with heparin and rheumatic children under salicylate treatment. The figures for increase in areas of spread with hyaluronidase in non-rheumatic cases were 226 to 285 sq. mm., and with distilled water 178 to 224 sq. mm.; in the cases of rheumatism being treated with salicylates the figures were 215 to 264 sq. mm. with hyaluronidase, and 195 to 237 sq. mm. with distilled water. The authors suggest that these differences indicate that salicylate has a greater anti-hyaluronidase effect than heparin. [The differences, however, are not statistically significant.]

W. A. Bourne.


Tests for the presence of C-reactive protein (C.R.P.) in the serum of 62 patients with rheumatic fever were carried out at Irvington House and New York University College of Medicine, the patients being grouped according to the stage of rheumatic activity as follows:

1. Active rheumatic fever, 35;
2. Low-grade rheumatic activity, 11;
3. "Doubtful activity", 11;

Observations were continued during treatment with
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various antirheumatic agents (including ACTH and cortisone) and during 6 months' convalescence. C.R.P. was present in the blood of nearly all the clinically active cases, and in six of the eleven doubtful cases, but was absent from all five cases of "pure chorea". Disappearance of C.R.P. from the blood is believed to indicate the termination of a rheumatic attack, while persistence of C.R.P. during treatment indicates inadequate suppression of the inflammatory process.

It is concluded that the presence of C.R.P. in the blood of a rheumatic patient is an extremely sensitive and reliable indication of rheumatic activity, but it is emphasized that its appearance is a non-specific response to many inflammatory processes. In certain isolated rheumatic conditions—for example, chorea, erythema marginatum, and subcutaneous nodules—there may be no C.R.P. in the patient's blood. Kathleen M. Lawther.


Ballistocardiograms were recorded at a U.S. Army hospital from eighteen young adult males suffering from acute rheumatic fever, thirteen of whom had clinical evidence of carditis. Of the 33 ballistocardiograms recorded from these thirteen patients, 31 were normal, one showed slight abnormalities, and one was considered dubious because of low voltage. Of twelve ballistocardiograms from five subjects without overt cardiac involvement, eleven were normal and one showed slight abnormalities. Records obtained when the activity of the disease was subsiding were normal in all but two cases. Case histories and ballistocardiographic tracings are presented.

The authors conclude that the ballistocardiogram is normal in most mild cases of rheumatic fever, even when there is clinical and electrocardiographic evidence of active carditis. J. F. Goodwin.


As part of a study undertaken at the University of Modena of the relation between the delaying effect of certain drugs on erythrocyte sedimentation in vitro and their anti-rheumatic action, the anti-rheumatic effects of the N-acetyl derivative of para-aminosalicylic acid (APAS) have been studied. The authors have also carried out experiments, chiefly pharmacological, on this substance, on the diacetyl derivative (DAPAS) and on the acid itself (PAS). APAS has the greatest effect on erythrocyte sedimentation, DAPAS has a mild effect, and PAS has none.

APAS was used in the treatment of eight cases of rheumatic polyarthritis in the acute phase, seven of the patients being in hospital and one an out-patient, the dose varying from 10 to 25 g. daily. In four cases salicylates had been given previously without effect. In all cases the effect of APAS was to reduce the temperature, and relieve the pain, while the signs of cardiac and respiratory distress abated. Signs and symptoms tended to recur if the drug was stopped too soon. When DAPAS was given the effects were the same, as was to be expected since, according to the authors, both DAPAS and PAS are transformed into APAS after ingestion to an extent which depends on a variety of circumstances.

Experimentally, both the sodium salt of APAS and sodium salicylate reduced artificially produced fever in rabbits, PAS being less reliable, but none of the PAS derivatives appeared to have any analgesic properties when tested on rats with infra-red radiation as the painful stimulus. It was shown that APAS (but not PAS) delayed the urinary excretion of phenyl-sulphonephthalein, which had previously been injected into the talocrural joint of a rabbit; this property is found also in sodium salicylate and other anti-rheumatic substances.

The author considers that the conflict of opinion on the value of PAS in rheumatism may stem from the fact that its therapeutic effect depends on the degree of its conversion into APAS, which may vary from 30 to 85 per cent. J. G. Jamieson.


Evidence is accumulating which supports the theory that rheumatic fever is caused by a tissue sensitivity reaction to some product of the Group-A β-haemolytic streptococcus. One of the two haemolysins produced by this organism, streptolysin S, is inhibited by a substance present in the serum of all individuals, sick or well, the inhibition being of a physico-chemical nature rather than the result of an antigen-antibody. The strength of this inhibiting substance varies from individual to individual, and is dependent in part on the concentration of the serum of phospholipid, one of the ingredients of which is choline. Since the body can neither synthesize nor store choline in any significant quantity, the serum phospholipid level must depend on the dietary intake of choline, by far the richest source of which is egg. The author therefore estimated the egg intake in childhood of 184 subjects with rheumatic heart disease and compared it with that of 1,380 unaffected persons interviewed at the Pennsylvania Hospital, Philadelphia. Of the affected subjects, 10-2 per cent. actively disliked eggs and 40-6 per cent. believed that their consumption of eggs in childhood had been relatively small, the corresponding figures being 4-6 per cent. and 16-3 per cent. respectively in the control group. It is suggested that this difference in probable choline intake might have a bearing on the difference in susceptibility to rheumatic fever between the two groups. R. S. Illingworth.


In a further study of the relation between the phospholipids in the serum and susceptibility to rheumatic fever the authors determined the serum phospholipid level in 178 patients with inactive rheumatic heart disease. It was found that the level was below the average for normal individuals of the same age group in approximately two-thirds of these cases. Of 51 patients who had had more
than one attack of rheumatic fever, 46 had either an unusually low serum phospholipid level or a history of an unusually low intake of eggs in childhood.

It is suggested that rheumatic fever may be produced “when a hemolytic streptococcal infection engenders more streptolysin S than the natural serum inhibitor, as a reflection of serum phospholipid, is able to neutralize”.

R. S. Illingworth.

A Follow-up Study of Suspected Rheumatic Fever Patients.
In the past 11 years 2,678 new patients have been seen in the Medical College of Virginia Rheumatic Fever Clinic. In this group, 236 were listed as “deferred” after a complete initial study. Follow-up data have been obtained on 209 of these 236 cases.

The complaints and suspicious signs which were the reason for deferral are listed and compared with those [occurring in the 29 patients] later developing clear rheumatic fever. [This comparison shows a significantly higher incidence in the latter group of painful joints with swelling, fever, epistaxis, suspicious choreiform movements, increased erythrocyte sedimentation rate, electrocardiographic abnormality, and tachycardia.]

After an average follow-up period of 28 months, the following diagnoses have emerged:

- Rheumatic fever . . . . 13.88 per cent
- (2.4 per cent. with rheumatic heart disease)
- Rechecked and no rheumatic fever or heart disease found . . 66.98 per cent.
- Local medical doctor says no rheumatic fever . . . . 9.09 per cent.
- Nurse says patient well . . . . 3.83 per cent.
- Diagnosis still deferred after recheck . . 6.22 per cent.

The excellent prognosis in this group as a whole makes strict diagnostic criteria imperative.—(From the author’s summary.)

Hormone Therapy in 22 Cases of Rheumatic Fever.
(Une expérience d’hormonothérapie dans la maladie de Bouillaud (22 cas.) Gaufroy, B. (1954). Rev. Rhum., 21, 35. 1 fig.


Lancet, 1, 529. 4 figs, bibl.

Chronic Articular Rheumatism
(Rheumatoid Arthritis)

Brit. med. J., 2, 1231. 5 figs, 22 refs.

In this epidemiological study, carried out by members of the Medical Research Council Pneumoconiosis Research Unit, of a syndrome recently described by Caplan (Thorax, 1953, 8, 29) in which rheumatoid arthritis is associated with nodular fibrosis of the lung, chest radiographs of miners in the Rhondda Fach, South Wales, were re-examined. From among those showing massive fibrosis or tuberculosis, all films (20) which were thought also to show “rheumatoid”-type opacities were selected, sixty other films not showing these characteristics being used as controls. The twenty miners from whom the characteristic films were obtained were visited, questioned, and their joints examined if the history suggested arthritis; the criteria for the clinical diagnosis of arthritis are given. In addition, all men considered (in a previous survey) to have rheumatoid arthritis, as well as the twenty selected as having “rheumatoid” radiological appearances in the chest, were fully investigated.

It was found that the incidence of rheumatoid arthritis was higher (3 per cent.) among miners having massive fibrosis or tuberculosis than among the general population (0.42 per cent.), while its prevalence in the group showing “rheumatoid” opacities in the chest film was 55 per cent. (No clinical evidence of rheumatoid arthritis was found in the whole series save in these two groups.)

The activity, severity, and duration of the arthritis was not correlated with the degree of typical “rheumatoid” radiological appearance. It was also noted that the rheumatoid lung lesions may either precede the onset of arthritis or develop subsequently. Total dust exposure may be a significant factor in determining the occurrence of rheumatoid arthritis, and it was noted that a high prevalence of arthritis occurred in men exposed to stone dust. Clinical examination of the group showed evidence of pulmonary tuberculosis in only one man.

One case in which the chest radiograph showed rheumatoid lesions came to necropsy during the investigation; the findings are detailed. The pulmonary lesions consisted of whorled, yellowish-white, collagenous fibrous tissue, with central softening but no evidence of tuberculosis, and resembled those described by Gough under the name of “infective nodules”. Although the findings at this necropsy did not confirm the presence of tuberculous infection, five other necropsies of men with rheumatoid arthritis (in whom the x-ray appearances were less typical) have yielded evidence of it. Also, from two men with “rheumatoid” chest lesions and proved tuberculosis, atypical bacilli were isolated, which produced tuberculosis on injection into guinea-pigs. The condition may therefore be one in which the tubercle bacilli are modified.

It is suggested that the hypotheses that:

(a) these appearances are coincidental and merely a manifestation of the rheumatoid syndrome,
(b) that the pathological changes play the part of a chronic septic focus,
are unlikely.

The authors conclude that there must be some other factor, and that the predisposition to form these lung lesions may be an expression of an unusual type of tissue reaction to dust and tuberculosis in miners who are predisposed to rheumatoid arthritis.

In previous communications (Brooklyn Hosp. J., 1950, 8, 148, and Amer. J. med. Sci., 1951, 222, 243; Abstracts of World Medicine, 1951, 9, 643, and 1952, 11, 81) these authors have reported the synergistic action of para-aminobenzoic acid, given by mouth, and cortisone acetate, given by intramuscular injection. In this paper from the Brooklyn Hospital, New York, they report the effects of the combined oral administration, over a period of one year or more, of cortisone acetate and the sodium or potassium salt of para-aminobenzoic acid to 31 patients with rheumatoid arthritis. Their impression is that combination with para-aminobenzoate increases the anti-inflammatory action of a given dose of cortisone acetate two to three-fold, and that such increased potentiation is not accompanied by a similar increase in the incidence of side-reactions or complications.

W. S. C. Copeman.


The purpose of the investigation here reported was to compare the effect of cortisone with that of compound codeine tablets (B.P.) in relieving the pain and curtailing the period of increased disability following the manipulation under a general anaesthetic of the flexed knees of patients suffering from rheumatoid arthritis. Four different centres took part, and 33 patients with flexion deformities of the knees of at least 6 months’ duration were admitted to the trial, eighteen receiving cortisone and fifteen the tablets. To both groups the drug was given on the day before manipulation, on the day of manipulation, and for 14 subsequent days. The dose of cortisone was 200 mg. on the first day, 300 mg. on the day of manipulation, and on the third day, 200 mg. on the fourth and fifth days, 150 mg. for the next 3 days, 100 mg. for the next 2 days, and 50 mg. for the last 6 days. Two compound codeine tablets were given 3 times a day to the other patients.

After manipulation the knee was put in plaster, which was bivalved after 24 hours, the posterior shell only being retained. Assessments of the patient’s condition were made on the 5 days before and 5 days after manipulation, and then at 5-day intervals until the 26th day after admission to the trial. The assessments were made by the same group of observers, and covered pain on pressure, pain on active and passive movement, range of movement, circumference of the knee, skin temperature, and the time taken to carry out complete flexion and extension five times with the heel supported on a skate in the horizontal position. From the results of the trial, which are given in the form of tables and a chart, it was concluded that “cortisone revealed no advantage over tab. codeine co. as a cover for manipulation of the knee”.

This report has evoked much discussion; it is important to note that the investigation was made only into the effect of these preparations on the sequelae of manipulation of a flexed knee, not into their effect on the disease as a whole.

W. Tegner.


Phenylbutazone was tried at Withington Hospital, Manchester, in the treatment of 186 patients with chronic polyarthritis of the rheumatoid type and 24 with degenerative hip disease. During the investigation, which did not include a control series of cases, other forms of treatment, including gold injections, were continued. In assessing the results the effect of rest in bed was discounted. The average dose of phenylbutazone was 600 mg. daily. Patients were examined before, and 3 and 6 months after, beginning treatment. Subjective improvement was judged by the patient’s capacity for, and comfort during, normal activity.

After 3 months’ treatment, the condition of 156 patients was reviewed. It was found that the drug was of “little or no value” in 36, of “moderate value” in 104, and of “considerable benefit” in sixteen. The erythrocyte sedimentation rate was apparently not affected. Toxic reactions occurred in 92 cases, about 25 per cent. of all patients having to cease treatment on this account. Reactions consisted in gastro-intestinal symptoms, including gastric haemorrhage, rash, oedema, fever, soreness of the mouth, and a few, infrequent manifestations of doubtful origin. There was no correlation between the serum level of phenylbutazone and the incidence of toxic reactions.

G. Loewi.


Clinical Study of Chrysotherapy in Rheumatoid Arthritis. (Contributo clinico alla cristeroterapia dell’artrite reumatoide.) FARNETI, P., and MICCOLI, G. (1954). Reumatismo, 6, 148. 1 fig., 37 refs.


MUSCULO-SKELETAL FUNCTION IN RHETMATOID ARTHRITIS.

NEUROVEGETATIVE INVESTIGATIONS IN RHETMATOID ARTHRITIS.
(Saggi neurovegetativi nell’artrite reumatoide.) Rossi, G. (1954). Reumatismo, 6, 182. 15 refs.

EARLY RADIOLOGICAL SIGNS OF RHETMATOID ARTHRITIS.

OSTEO-ARTHROISIS.

RECOGNITION AND MANAGEMENT OF DEGENERATIVE JOINT DISEASE.

OSTEO-ARTHRITIS OF THE HIP. DIAGNOSIS AND TREATMENT.

EFFUSION INTO THE JOINT IN OSTEO-ARTHRITIS OF THE KNEE.

SPONDYLITIS.
UNRECOGNIZED LATE FORMS OF BECHTEREW’S DISEASE.

This study was carried out at the Balneological Institute at Bad Nenndorf where, it is claimed, some 200 cases of ankylosing spondylitis are treated every year. Of 195 cases referred for treatment in 1952, twelve had been either misdiagnosed or only belatedly recognized. On going into the reasons for this delay in diagnosis it was found that twelve patients could be divided into four groups, case histories representative of each being given. In the first group pain was not a prominent feature and attention had finally been drawn to the spine by increasing deformity; in the second group a polyarthritis had overshadowed the spinal signs and symptoms; in the third group an industrial accident had been held responsible for symptoms which would otherwise have been investigated more closely; and in the last group the symptoms distributed over various parts of the spinal column, were so mild that they had been ascribed to “muscular rheumatism”.

Treatment in such long-standing cases should be both general and local, gold injections and x-ray therapy being suggested; breathing and remedial exercises are also advisable. Balneotherapy is regarded as an ideal combination of general and local treatment, but must be continued for many years until the disease process is finally arrested.

ANKYLOSING SPONDYLITIS AND PULMONARY TUBERCULATION.
(Spondilitis anchilosante e tubercolosi polmonare.) BARBOSO, E., and EINAUDI, G. (1954). Reumatismo, 6, 176. 19 refs.

(MISCELLANEOUS)
EFFECT OF SPLENECTOMY IN ACUTE SYSTEMIC LUPUS ERYTHEMATOSUS.

The author reports the results of splenectomy in twelve cases of acute systemic lupus erythematosus seen in Hawaii, where the disease is common among the Japanese and Chinese inhabitants. He points out that hyper-splenism is the probable cause of the thrombocytopenia, granulocytopenia, and anaemia which are sometimes very severe in this disease, and that these haematological manifestations constitute the main indications for splenectomy.

In two cases the operation was performed as an emergency for acute thrombocytopenic purpura; after operation there was complete cessation of the haemorrhagic tendency, with dramatic clinical improvement. Anaemia and leucopenia were present in the remaining ten patients, two of whom also had thrombocytopenia, and splenectomy was performed during the active phases of the disease “as a desperate measure”. Three of these patients died within 10 days of operation; in the remaining seven there was a varying degree of symptomatic relief which, however, was maintained in only two. All but four of the twelve patients died from lupus erythematosus within one year of operation; one died 2½ years after operation, but three were alive, 7, 3, and 2 years later respectively.

The operation was followed by an increase in the erythrocyte, leucocyte, and platelet counts. Histological examination of the spleen, which was enlarged in eight of the cases, showed concentric parieto-ilar collagen lamination, sinus hyperplasia, and widened marginal zones of medium and large lymphocytes at the periphery of the Malpighian follicles.

[The majority of these cases were seen before the introduction of the L.E.-cell and L.E.-plasma tests, and the diagnosis was based upon the association of fever, polyarthritis, rashes, leucopenia, anaemia, thrombocytopenia, and albuminuria.] Nigel Compston.

TREATMENT OF LUPUS ERYTHEMATOSUS WITH CHLOROQUINE SULPHATE.

Thirty cases of lupus erythematosus were treated with chloroquine sulphate (“nivaquine”). The results obtained were as good as those from mepacrine hydrochloride (“atabrine”). The drug is much less toxic and so far has caused no dermal complications. The mode of action of chloroquine sulphate is unknown but future lines of investigation are suggested.—[Authors’ summary.]
ABSTRACTS


The authors reserve the term "developmental dysarthria" for dysarthria which is not associated with neuromuscular disorders elsewhere, as in spastic diplegia. Boys are affected twice as often as girls, and in ten out of eighteen cases examined at the Royal Victoria Infirmary, Newcastle upon Tyne, there was a family history of a speech defect. Birth injuries, prematurity, and emotional disturbances do not appear to be responsible. In two-thirds of the authors’ cases voluntary movements of the tongue, lips, or palate were manifestly spastic, but in the remaining one-third the abnormality of movement occurred only during speech, and these cases the authors regard as examples of "articulatory dyspraxia". Although the intelligence of the eighteen children studied was within the range of normal, in half of them there had been some delay in the development of language. The speech in cases of developmental dysarthria is slow, clumsy, and often explosive, and the response to treatment is usually slow. This is in marked contrast with cases of dyslalia, a term reserved by the authors for instances of temporary consonant substitution, in which language develops at the normal time, speech is fluent if unintelligible, and the response to treatment is rapid.

J. Foley.


The relation between the blood level of phenylbutazone given by mouth and the toxic and therapeutic effects was investigated at the West London Hospital, Hammersmith, in 52 patients, 48 of whom had rheumatoid arthritis and four had osteo-arthritis.

The blood level of phenylbutazone varied considerably in different patients on the same daily dosage. The average level, however, rose steadily when the dosage was increased, up to a maximum of 600 mg. daily; when it was increased beyond this to 1,200 mg. the blood level rose less quickly. Toxic effects were noted in 25 patients, but were mild in fifteen and did not call for cessation of treatment. There was a marked and statistically significant correlation between the incidence of side-effects and the blood level of the drug; when the blood level of phenylbutazone was more than 10 mg. per 100 ml. the incidence of side-effects was high (85 per cent.). One patient died from renal failure, possibly precipitated by the salt-retaining effect of phenylbutazone.

No objective improvement was observed in any of the patients, and the authors therefore had to rely on the subjective response to assess the therapeutic effect of the drug. On this basis, they found that when the blood level was below 5 mg. per 100 ml., two out of eight patients obtained relief of symptoms; when the level was between 5 mg. and 10 mg. per 100 ml., 25 out of 29 patients experienced relief of symptoms. At blood levels above 10 mg. per 100 ml. the therapeutic effect was not notably enhanced.

In another investigation the authors found that the blood level of phenylbutazone rose slowly, reaching a maximum in about 10 days. The drug was retained in the body, and when administration ceased, excretion continued for 10 to 21 days. Toxic effects may therefore persist or may even appear after the drug has been discontinued.

The authors consider that phenylbutazone is most effective at a blood level of 5 to 10 mg. per 100 ml., but because of individual variations in absorption a fixed scheme of dosage cannot be laid down. They suggest that a dose of 200 mg. daily should be given initially, increased by 100 mg. daily until the response is satisfactory. With doses of more than 400 mg. daily the likelihood of serious toxic reactions increases rapidly.

B. E. W. Mace.


The authors report their results in 700 cases of rheumatism which, since January, 1952, they have treated with phenylbutazone given parenterally. The conditions for which the drug was administered included gout, rheumatoid arthritis and spondylo-arthritis, tendinitis and tendino-bursitis, arthroses, and radiculalgia. The general plan of treatment was to begin with a course of intravenous infusions of 1 g. phenylbutazone in a 10 per cent. solution given daily, or on alternate days. As symptoms subsided, usually in the second week of treatment, intramuscular injections of a similar dose of phenylbutazone, with triethylene glycol and procaine, were substituted for the infusions, and these were also given daily or on alternate days. Subsequently, the intervals between injections were gradually increased, until for chronic cases individual maintenance doses were established.

The best results were observed in cases of gout and ankylosing spondylitis. In cases of rheumatoid arthritis they were inconstant. With adequate dosage, the maximum effect of the drug was observed from the beginning of treatment. The authors regard the following three precautions as indispensable:

1. The patients should be carefully selected, cachectic cases and those having an abnormal blood picture or a history of gastric and cardio-renal disease being excluded;
2. During treatment a strict sodium-free diet must be enforced;
3. Treatment should be suspended at the first sign of complications, such as digestive disturbances, peripheral oedema, haemorrhage, or cutaneous eruptions.

A. Swan.


"Stigmonene" bromide is a synthetic alkaloid-like salt of the quaternary pyridinium series having a slightly less powerful cholinergic action than neostigmine but the advantage of being of lower toxicity. This drug was given parenterally in doses of 0·5 to 4 mg. twice weekly to 64 out-patients attending St. Vincent’s Hospital, New York, for the treatment of muscular spasm associated...
with osteo-arthritis, rheumatoid arthritis, and allied conditions.

Increased range of joint movement and decrease of pain was obtained in thirty (53 per cent.) of 55 patients followed up, and this improvement was maintained in eleven (61 per cent.) of eighteen treated during the following 10 weeks with saline injections as a placebo. Side-effects, which were minimal and were relieved by oral administration of atropine, included abdominal distress, paraesthesiae, muscular weakness, aggravation of the arthritis (two cases), and syncope (one case, doubtfully attributable to the stigmene). It is emphasized that these cases were far advanced and unlikely to respond dramatically to any form of therapy. The optimum dose of the drug was considered to be 3 or 4 mg. twice weekly.

I. Ansell.


Disk Syndrome


Gout


It has been claimed that phenylbutazone causes a striking diminution in the serum uric acid level in acute gout. The author has studied the effect of the drug in five cases of acute gout at Chase Farm Hospital, Enfield, Middlesex. He states that a specific effect on uric acid metabolism and on acute gout would be unique.

In the first case administration of 600 mg. daily of phenylbutazone resulted in a fall in the blood uric acid level from 11.6 mg. to 4.3 mg. per 100 ml. by the tenth day; there was excess excretion of uric acid amounting to 1,485 mg. during the 10 days.

In the second case the serum uric acid level fell from 4.7 mg. to 3.5 mg. per 100 ml. in 7 days, the excess uric acid excreted being 620 mg.

In the third case the total excess of uric acid excreted was 2,254 mg. in 7 days, but the serum level fell only from 5.4 mg. to 4.8 mg. per 100 ml.

The plasma uric acid level did not fall in the fourth case, in which, moreover, an actual retention of 365 mg. uric acid was observed; there was appreciable water retention in this case.

The fifth patient had Paget's disease, but during the first week of phenylbutazone therapy the plasma uric acid level fell from 4.9 to 2.6 mg. per 100 ml. and the uric acid excreted amounted to 686 mg.

In the second, third, and fifth cases, the fall in the uric acid concentration in the serum was roughly equivalent to the amount excreted, assuming equal distribution in the body water, but in the first case the fall in the serum level was much greater than could be accounted for by the urinary excretion. It is suggested that the variable results were due to the water-retaining and uricosuric properties of the drug, and that a direct effect on uric acid metabolism has not been proved.

C. L. Cope.


Non-Articular Rheumatism


Encouraged by the good results obtained with cortisone in the treatment of ten cases of periarthritis of the shoulder which had failed to respond to physiotherapy, the author extended this treatment to fifty similar cases, the results being reported in this paper from the Mayo Clinic. The drug was given by mouth in a dosage of 75 mg. a day for 3 to 4 weeks; in some cases, however, the
Pseudo-Polyarthritides of the Shoulder and Hip Girdles.
To the syndromes classed as “inflammatory rheumatism” the authors add one which they name pseudo-polyarthrite rhizomèle. This account of the condition is based on a study of 25 patients—seventeen women and eight men. Pain in both shoulders, abrupt in onset and preventing by its extreme severity all movement at the joints, associated with a lesser degree of pain and stiffness in the hips, a low-grade fever, and some loss of weight, are the most prominent clinical features of the syndrome, which affects individuals in the second half of life. It differs from the common scapulo-humeral periartitis in being bilateral and symmetrical, and in its association with fever, loss of weight, raised erythrocyte sedimentation rate (E.S.R.), and pain and stiffness in the hips. It is not a form of rheumatoid arthritis, from which it differs strikingly in its localization exclusively to the roots of the limbs and in its evolution: there is no spread to other joints, the tendency being towards complete recovery with no residual signs. Also, by its clinical features and evolution it is readily distinguished from ankylosing spondylitis and from the shoulder-hand syndrome.

Treatment with copper and with gold has been tried. In cases of recent onset, intravenous “cuprelene” was given intravenously in doses of 250 mg. twice weekly to a total of 2 to 3 g. Nearly all the patients so treated improved rapidly, the E.S.R. falling to normal within a few months. Others were treated with equally good results, with “aloxhrysine” in doses of 100 mg. weekly to a total of 1 to 1.5 g. in each course, with an interval of 6 to 8 weeks between the courses. Improvement was marked during the first course; by its end, pain had disappeared, the E.S.R. was normal, and only some slight stiffness of the shoulder remained. In all cases, cure resulted after one or two courses.

[Information concerning the course of the untreated disease would be helpful.] Kenneth Stone.

The results of treatment of “Frozen” shoulders by manipulation under anaesthetic (Penitothal), with ACTH or cortisone given concurrently, are described. Of 29 shoulders treated, in 26 patients, ten regained normal function, thirteen were improved, and six were unimproved; the results were not significantly different, in those cases with a definite inflammatory or traumatic origin, to those occurring spontaneously.
The authors noted that their good results tended to occur in patients who presented a definite clinical picture of disuse stiffness following an acute episode of pain, followed by partial recovery of movement, and by a single, definite release of resistance at manipulation. They postulate that the syndrome is due to adhesion of the capsule of the shoulder joint, in its antero-inferior region, and suggest the term “checkrein shoulder”.

Pain after manipulation was satisfactorily controlled by 40 mg. ACTH gel twice daily, for three days, or by oral cortisone, 300 mg. daily for 3-4 days, and then tapered off. Intensive active movements, together with exercises against resistance, were begun immediately after manipulation, interspersed with periods of rest, with the hands clasped behind the head. It is stressed that manipulation should be a gentle procedure, and should not be undertaken lightly.

B. E. W. Mace.


General Pathology
It has been suggested by Archer (Ann. intern. Med., 1951, 34, 1173) that the impairment of hepatic function frequently reported to occur in rheumatoid arthritis may well be due to the therapeutic agents commonly employed, many of which are hepatotoxic. The present authors describe their findings in seventeen cases of rheumatoid arthritis in men, who were subjected to needle-biopsy of the liver and various tests of hepatic function. They found no significant evidence of hepatic damage, even when the disease was of many years’ standing.

A. C. Lendrum.

The negative results of blood culture in many cases of
subacute bacterial endocarditis and most cases of rheumatic carditis are due, in the author's opinion, to the fact that the media commonly used do not meet the biological requirements of slow-growing micro-organisms capable of splitting carbohydrates with the formation of acid, since this acid, if allowed to accumulate, soon reaches a lethal concentration.

However, if media which contain natural albumin, such as Löwenholtz's broth, semi-liquid agar with plasma, or Tarozzi's medium, are used and the cultures incubated for periods up to 2 months, Staphylococcus viridans can be isolated in a very much higher proportion of cases. Thus the author was able to isolate Strep. viridans in thirty out of 36 cases of subacute bacterial endocarditis (83-3 per cent.), in eleven out of eighteen cases of primary or recurrent rheumatic carditis (61·1 per cent.), and in seventeen out of 43 cases of other forms of rheumatism.

These findings make it possible to regard all these diseases as of common aetiology. The isolation of the infecting organism is of importance also in the treatment of rheumatic diseases, as by determining its sensitivity the rational dose of penicillin can be ascertained.

H. W. Swann.


The effect of blocking the reticulo-endothelial system in the guinea-pig on the peripheral eosinopenia normally produced by the injection of ACTH (corticotrophin) was investigated in experiments carried out at the Medical Clinic of the University of Zurich. Blocking was achieved by the subcutaneous injection of a 1 per cent. aqueous solution of trypan blue, which is stored in the reticulo-endothelial system, 2 ml. being given on the first day and then 1 ml. every other day up to a total of 18 ml. Male guinea-pigs of 500 to 700 g. were used, some with a normal eosinophil count (up to 360 per c.mm.), some with a constant increase up to 6,600 per c.mm. ACTH (10 units) or cortisone (0-625 mg./100 g. body weight) was given 24 hrs after the last injection of trypan blue, and changes in the eosinophil count compared with those in a significant number of control animals which had not received trypan blue. The experiments were planned and evaluated statistically.

It was found that the eosinopenic effect of ACTH and of cortisone was diminished considerably by blockade of the reticulo-endothelial system, or even suppressed entirely. When the dose of cortisone was increased to 2·5 mg./100 g., however, a significant fall in the eosinophil count was achieved even in animals treated with trypan blue.

This effect, being obtained with cortisone as well as ACTH, must be independent of the adrenal cortex. It is thus concluded that the reticulo-endothelial system plays an important part in the mechanism of the eosinopenia caused by glucocorticosteroids.

V. C. Medvei.


The investigation here reported was undertaken at the Frederiksberg Hospital, Copenhagen, to determine whether the number of eosinophil granulocytes in the bone marrow changes when the eosinophil count in the blood decreases under the influence of ACTH (corticotrophin). At the same time a study was made of the relation between the eosinophils of the blood and bone marrow under normal conditions, about which there has been considerable difference of opinion. For the latter purpose specimens of blood and bone marrow from 31 patients were examined; eight of these were suffering from allergic disorders (six from asthma and two from drug eruptions), while the remainder had various diseases, none of which was likely to affect the eosinophil count. It was found that a low count in the blood (expressed as percentage of the total leukocyte count) corresponded to a low count in the marrow (expressed as percentage of all nucleated cells), and that when the count was increased in the blood, there was also a higher count in the marrow. In the five patients whose blood showed the highest eosinophil counts the percentage was lower in the marrow, whereas in the remainder the marrow count was consistently slightly higher. The effect of ACTH was then observed on thirteen of the same patients, including the six asthmatics, blood and bone marrow specimens being examined 4 to 6 hours after a single dose of 20 to 40 mg. ACTH, in nine cases also after a 3 days' treatment with 20 mg. three times daily, and in one case also before and after a dose of cortisone. The eosinophil values were expressed as in the previous series as a percentage of the total leukocyte or nucleated-cell count. It was found that 4 to 6 hrs after the dose of ACTH the eosinophil count in the blood was decreasing, while that in the marrow was rising. The initial rise did not persist, however, and after 3 days' treatment the eosinophil count in the marrow was in no case greater than it had been before the ACTH had been given.

V. C. Medvei.


In this well-controlled study carried out at the University of Illinois College of Medicine, Chicago, by means of clinical observation, measurement, and histological examination of biopsy specimens of the subcutaneous nodules of rheumatoid arthritis it was shown that these nodules are commonly softened and reduced in size by the administration of cortisone, but that even over long periods of administration of the hormone there appeared to be no consistent modification of the histological picture.

A. C. Lendrum.


ACTH, Cortisone, and Other Steroids


It has been shown that ascorbic acid depresses the sensitivity to tuberculin (as measured by the size of the skin reaction) of guinea-pigs injected with B.C.G., and that this desensitizing action is antagonized by a factor present in cabbage which apparently prevents the oxidation of ascorbic acid to dehydroascorbic acid; this factor is in turn antagonized by cortisone, which thus permits the decrease in sensitivity brought about by ascorbic acid to take place. Further experiments carried out at the National Institute for Medical Research, London, have shown that skimmed milk has properties similar to those of cabbage, as also has methionine, which is present in both. On the other hand ethionine, an antimetabolite to methionine, antagonizes the action of cabbage and skimmed milk in the same way as cortisone. The "cabbage factor" and the similar factor present in skimmed milk are therefore thought to be probably identical with methionine.

By analogy with the action of alloxan in diabetes, the author presents the hypothesis that cortisone depresses sensitivity to tuberculin in the guinea-pig by interfering with the anabolism of glutathione. The resulting fall in glutathione concentration in the tissues would increase the oxidation of ascorbic acid to dehydroascorbic acid, which inactivates phosphoglucomutase, resulting in an increase in the tissue concentration of glucose-1-phosphate, which has a desensitizing influence.

H. Herxheimer.


It has been shown that the effect of a dose of ACTH (corticotrophin) on the ascorbic acid content of the rat's adrenal glands is prolonged and enhanced if the ACTH is given together with polyphloretin phosphate, an effect which has been attributed to the anti-enzymatic properties of the latter compound. To test this assumption the author has compared the effect obtained when ACTH and polyphloretin phosphate were given separately with that obtained when the two substances were incorporated in one injection.

Male rats were subjected to hypophysectomy and, on the following day, to unilateral adrenalectomy. The drug or drugs were then given, and 1 to 24 hrs later the remaining adrenal gland was removed, the two glands being separately weighed and their ascorbic acid content assayed. Four groups of rats were treated as follows:

1. ACTH alone (0-1 unit/100 g. body weight);
2. ACTH + polyphloretin phosphate (2 mg./100 g.) as a freeze-dried complex dissolved in saline;
3. ACTH and polyphloretin phosphate given as separate intramuscular injections;
4. ACTH parenterally and polyphloretin phosphate (10 mg./100 g.) by mouth.

It was found that the enhancement of activity of the ACTH was quantitatively the same however the polyphloretin phosphate was given, though the substance itself had no effect on the adrenal ascorbic acid content either in hypophysectomized or in intact rats. These results are held to indicate that polyphloretin phosphate protects ACTH from inactivation in the tissues. Whether the mechanism of this action is anti-enzymatic in nature is not indicated by these experiments, but this seems the most likely explanation.

Nancy Gough.


The efficiency of the reticuloendothelial cells (Kupffer's cells) to engulf bacteria appears to be about equal in the rats treated with large doses of cortisone and in normal rats, but the ability of these cells in the treated animals to destroy the engulfed organisms is definitely depressed. This depression of the reticuloendothelial cells may be an important factor in the increased susceptibility to infection in animals treated with large doses of cortisone.—[Authors' summary.]


Cortisone is known to aggravate various infections in man and animals, probably by depressing the host's defence mechanisms. In the present study, undertaken at the University of California School of Medicine, San Francisco, in order to determine whether this action of cortisone might impair the therapeutic efficacy of antibiotics, groups of white mice were infected with Klebsiella pneumoniae and subsequently treated by the injection of either streptomycin or aureomycin for 3 days.

In the groups of animals which also received cortisone treatment, starting 24 hrs before infection, the cure rates were usually lower than in those not given cortisone. The impairment was most apparent when the dose of antibiotic was barely curative when given alone; for example, 2 mg. aureomycin reduced the mortality from 100 per cent. to 12 per cent., but when 1 mg. cortisone and 2 mg. aureomycin were given the mortality was 72 per cent. If sufficient antibiotic was injected, however, the cure rate was not reduced by the administration of cortisone at the same time. These findings, which were
equally true of the bacteriostatic drug, aureomycin, and of the bactericidal drug, streptomycin, are in keeping with the view that the host's defence mechanisms contribute materially to the curative action of antibiotics, and that these mechanisms are depressed by the action of cortisone.

Derek R. Wood.


The disappearance of ascorbic acid from the adrenal cortex on injection of corticotrophin (ACTH) has been noted by a number of workers in various different species of animals. But whether the ascorbic acid is consumed within the cortex or extruded into the plasma has never been clearly demonstrated. At St. Thomas's Hospital, London, therefore, the authors investigated the changes in the quantity of reduced ascorbic acid and its immediate oxidation products in the plasma and urine of patients treated with ACTH and in the urine of guinea-pigs given injections of the hormone.

The reduced ascorbic acid value was determined by titration with dichlorophenolindophenol; direct determination was made in the case of plasma, but for urine, which contains interfering substances, the "formaldehyde correction" procedure developed by Snow and Zilva (Biochem. J., 1944, 38, 458) was followed. The amounts of the immediate oxidation products of ascorbic acid, namely, dehydro-ascorbic acid and diketogulonic acid, were also determined, the former by reduction with hydrogen sulphide and the latter by the method of Roe and Kuether (J. biol. Chem., 1943, 147, 399).

Six patients receiving treatment with ACTH were studied. All were given a diet containing no more than 40 mg. of ascorbic acid per day, which was supplemented in two cases by 300 mg. per day and in one case by 30 mg. per day. After a stabilization period and before administration of ACTH, two of the patients were found to have a high initial ascorbic acid level in the plasma (greater than 1 mg. per 100 ml.), two had an intermediate initial level (0·75 to 1·0 mg. per 100 ml.), and two a low initial level (less than 0·6 mg. per 100 ml.). The patients with high and intermediate initial levels responded similarly to administration of ACTH, showing increased output of ascorbic acid in the urine for the first 2 or 3 days only; the dehydro-ascorbic acid output was also increased in one case but not in the others. Plasma determinations showed a tendency for the levels of oxidation products of ascorbic acid to rise at first and then fall with continued therapy. The findings in guinea-pigs with adequate intake of ascorbic acid were similar. Patients with low ascorbic acid saturation did not, however, show these changes.

Three possible mechanisms are suggested and discussed, namely, increased renal clearance of ascorbic acid, a passive shift of ascorbic acid from cells to extracellular fluid with the usual shift of water, and a further transfer of ascorbic acid in the same direction due to some unidentified mechanism.

Nancy Gough.


In order to confirm the finding of Selye (Canad. med. Ass. J., 1951, 64, 489; Abstracts of World Medicine, 1951, 10, 523) that pituitary somatotrophic hormone can counteract the development of lowered resistance to infection caused by overdosage with ACTH and cortisone, the authors, working at the Institute of Experimental Medicine and Surgery, University of Montreal, carried out four experiments on rats the results of which are here described.

In the first experiment, it was shown that the development of bacterial infection and the mortality from such infection were clearly promoted by the administration of cortisone in doses of about 20 mg. daily; and that this effect of cortisone could be counteracted by the simultaneous administration of pituitary growth hormone. In the second, it was shown that growth hormone had no effect on connective tissue, as measured by the rate of migration of subcutaneously injected haemoglobin. In the third, it was established, mainly by observations of changes in body weight of the animals, that the protective effect of growth hormone was not part of its general anabolic properties. In the fourth experiment, they showed that growth hormone was less able to prevent infection in adrenalectomized rats. Finally, it was established that neither testosterone propionate, deoxy- cortone acetate, nor oestradiol possessed the "anti-infection" properties of growth hormone. B. Nordin.


In this study of the nephrosclerosing action of hydrocortisone, alone and in combination with pituitary somatotrophic hormone, carried out at the University of Montreal, 24 male rats were divided into four groups. The first group acted as a control, the second received 2·5 mg. of hydrocortisone subcutaneously daily, to the third pituitary growth hormone was given three times daily subcutaneously, and the fourth group received both substances. At the end of 3 weeks the animals were killed and examined.

It was confirmed that hydrocortisone produced severe loss of weight, atrophy of the adrenal and thymus glands and of the spleen, mild glomerular lesions, slight elevation of the blood pressure, and necrotic foci in the lungs. Growth hormone did not prevent the adrenal and thymic atrophy and it aggravated the renal lesions, but it did prevent the appearance of infected foci in the lungs and also the severe loss of weight. The possible mechanism of this action is discussed and several hypotheses are proposed.

B. Nordin.
Prolonged Cortisone Therapy in the Congenital Adrenocortical Syndrome. (Die Cortisondauerbehandlung des konigenitalen adrenogenitalen Syndroms.) Prader, A. (1953). Helv. paediat. acta, 8, 386. 14 figs, 46 refs.

The report describes the results of the treatment with cortisone of ten female and four male patients with congenital adrenocortical hyperplasia. The ages of the females ranged from 3 to 30 years, and of the males from 6 to 36. Six of the former had undergone unilateral adrenalectomy without improvement, followed by oestadiol implantation in doses ranging from 40 to 280 mg.; six (four of them under 14) had undergone amputation of the enlarged clitoris; and three had received a short course of cortisone some time previously.

All fourteen patients were treated with cortisone for periods of 3 to 20 months (average 13 months). The drug was given by mouth in three doses totalling 25 to 75 mg. daily, intramuscularly in doses averaging 75 mg. every fourth day, or in the form of "depot-cortisone", a long-acting suspension of cortisone crystals up to 100 µg in size, of which a single injection of 600 to 900 mg. was given monthly. The clinical effects were identical with all three methods of administration, and there were no side-effects in the two cases treated with depot-cortisone. The dosage was adjusted to that which kept the urinary excretion of 17-ketosteroids just below 8 mg. daily in the older patients, and which caused minimal inhibition of growth in the younger patients. Some of the patients were admitted to hospital for the first 2 or 3 weeks, but for the most part treatment was given at home, the patients sending urine for 17-ketosteroid estimations and attending as out-patients every 2 or 3 months. Sodium intake was not restricted and no extra potassium was given.

The treatment was uniformly successful, the main results being as follows:

1. acne disappeared within a few weeks;
2. within 1 to 3 months the older girls became more feminine in appearance and their breasts developed;
3. the testicles of the older boys began to mature and testicular tumours became smaller;
4. hirsuties regressed in the older girls and did not develop in the younger children;
5. the pitch of the voice rose in the older girls;
6. marked pigmentation disappeared;
7. increased rate of growth and of skeletal development in the younger children was prevented;
8. the haemoglobin value, if increased, became normal;
9. the psychological effects of the glandular disturbance were improved;
10. menarche occurred, usually within 7 months.

No untoward side-effects were seen, even after 20 months' treatment. When treatment was stopped, however, recurrence of symptoms was the rule. The author recommends that treatment be started early in childhood and continued for years, strict supervision in regard to 17-ketosteroid excretion, blood pressure, growth, and weight being essential. With older patients, the desirability of treatment must be decided on its merits in each case.

V. C. Medvei.


The results achieved with cortisone in the treatment and maintenance of eight patients with Addison's disease and three with hypopituitarism, who were followed up at the Radcliffe Infirmary, Oxford, over a period of 18 months, are briefly summarized. Most of the patients with Addison's disease had received deoxycortone acetate and salt previously, and the addition of cortisone usually resulted in the dosage of the former being halved. For maintenance, 10 to 25 mg. cortisone was given daily in four divided doses, but much larger amounts were required during crises. In most cases appetite improved and the patient experienced a sense of well-being and an increase in initiative and vigour. In six of the patients with Addison's disease there were healed or active tuberculous lesions but cortisone did not appear to affect this condition.

A. C. Crooke.


The authors, working at the Postgraduate Medical School of London, have assessed the response of the adrenal glands to stimulation by ACTH (corticotrophin) given by various routes by measuring the changes produced in the plasma content of 17-21-dihydroxy-20-ketosteroids (such as hydrocortisone, cortisone, and their metabolic reduction products). The method of assay used by the authors has been described elsewhere (Biochem. J., 1953, 54, 523).

The drug was administered by intravenous infusion to twelve subjects, only two of whom "were not clinically ill at the time of study", the remainder suffering from a variety of diseases. An increase in the plasma steroid level appeared within 15 to 30 min. of starting the infusion, the level reaching its maximum in most cases within 1 hr. and remaining fairly constant during the infusion, and falling rapidly after its completion. A maximal response was obtained in most cases with a dose of one unit ACTH per hour for 6 to 8 hours, the plasma steroid level rising to between 24 and 36 µg. per 100 ml. After repeated daily infusions in two cases a higher level was obtained suggesting that repeated stimulation of the adrenal cortex increases its hormone output. A single intramuscular injection of 80 units ACTH in gelatin ("acthar" gel) was given to seventeen patients, "all of whom were comfortable at the time of study, except three with asthma". The plasma steroid level began to rise within 2 hrs and reached its maximum between 4 and 8 hrs after the injection, falling to normal in most cases within 12 to 24 hrs. Injections of 20 units ACTH in acthar gel produced a more transient elevation of the plasma steroid level, although in some cases the maximum level reached did not differ significantly from that obtained with 80 units. In five cases in which repeated injections of acthar gel were given there was again a progressively increasing response.

A single intramuscular injection of ACTH dissolved in
saline was given to sixteen patients, eight of whom were "clinically ill", the maximum response being obtained after 1 to 2 hrs and the effect of the injection passing off within 4 to 6 hrs. The degree of response was very variable, however, and in two cases was negligible.

It is concluded that intravenous infusion is probably the most reliable, and certainly the most economical, method of administration of ACTH. Nigel Compston.


The action of cortisone has been studied on the heterologous transplantation, growth, and metastatic diffusion of a transplantable adenocarcinoma in DBA mice, and on the genesis, growth, and metastatic diffusion of tumors induced in the skin and subcutaneous tissues of Swiss mice with methylcholanthrene. Cortisone did not show any appreciable influence on the heterologous transplantation of a mammary adenocarcinoma from DBA mice and on the growth of methylcholanthrene-induced tumors in Swiss mice. The growth rate of a transplanted adenocarcinoma in DBA mice was temporarily inhibited by the administration of cortisone. The induction of skin tumors in Swiss mice by methylcholanthrene has been markedly inhibited by the administration of 0.5 mg. of cortisone daily. Cortisone has been found to favor an increased metastatic spread of all the experimental tumors studied. —[Authors' summary.]


ACTH and cortisone were tried at Rhode Island Hospital, Providence, in the treatment of five cases of keloid formation. A female aged 17 had undergone bilateral mastoidectomy at the age of 4, after which keloids formed behind both ears. Radiotherapy was given and later the keloids were excised. When she was seen some years later a large keloid was observed on each of the original sites. She was given an intramuscular injection of 25 mg. ACTH, the keloids were excised, and ACTH in a dose of 20 mg. was injected 6-hrly thereafter. The result was satisfactory, only a very small tumour reappearing behind the left ear. Keloids on the abdomen and knee were unaffected. A woman aged 28 had keloids on the chest on the site of old acne lesions; these recurred after excision and radiotherapy. She was given 25 mg. cortisone by mouth three times a day for 3 weeks, and cortisone ointment containing 16-6 mg./g. was applied for a month. She complained of pain and irritation in the scars; the keloids reformed, and during the following 3 months they increased in size and symptoms became more severe. In two cases keloids appeared where the lobes of the ears had been pierced. In one of these patients, a girl aged 14, they were excised and cortisone ointment was applied for 2 months, but the keloids reformed. In the fifth case in the series a keloid appeared at the site of an injury to the neck of a girl aged 11. It was excised and cortisone ointment applied, but the growth occurred.

The authors conclude that surgery with radiotherapy remains the treatment of choice in this condition.

**E. Lipman Cohen.**

**Mode of Action of Sodium Pyrocatecholcarboxylate and Sodium Diacetylpyrocatecholcarboxylate and of their Synergism with Cortisone in the Rat.** (Étude du mode d'action du pyrocatechol carboxydale de soude et du diacetyl pyrocatechol carboxydale de soude et de la synergie cortisone pyrocatechol carboxydale de soude chez le rat.) Michotte, L. J., Levis, S., and Dauby, J. (1953). Rev. Rhum., 20, 743. 1 fig, 12 refs.

This paper from l'Union Chimique Belge describes work designed to throw light on the mode of action of sodium pyrocatechol carboxydale and its diacetyl derivative. The authors have compared the effects of these compounds with that of sodium salicylate, cortisone acetate, and ACTH when injected into intact rats, hypophysectomized rats, and adrenalectomized rats, in doses which produce a marked eosinopenia in intact rats. The eosinophils were counted before and after the administration of the test substances, the intact rats being given Nembutal so that no stress-reaction should interfere. These experiments showed that the eosinopenia produced by sodium pyrocatechol-carboxydale and its derivative was not dependent on the presence of either the hypophysis or the suprarenal gland. Furthermore, these compounds had no effect on the adrenal ascorbic acid and had no power to prolong the survival time of rats exposed to cold-stress.

Epinephrine, which also produces a fall in the blood eosinophils in adrenalectomized rats, seemed to react synergistically with cortisone; that is, doses of epinephrine and cortisone, each too small to produce eosinopenia alone, caused a significant fall if administered together. In the same way, sodium pyrocatecholcarboxydale and its diacetyl derivative show synergism with cortisone, so that a dose one-quarter the minimum active amount of cortisone can produce eosinopenia and protection against cold-stress in the adrenalectomized rat. Hence sodium pyrocatecholcarboxydale can replace epinephrine in the physiological complex cortisone-epinephrine.

**Nancy Gough.**


After commenting on the great variety of treatments which have been advocated for periarthritis of the shoulder the authors maintain that whereas cortisone gives results which are in no way superior to simpler, cheaper, and less dangerous forms of therapy, hydrocortisone on the other hand gives excellent results on local injection and is the treatment of choice. Of fifty cases so treated at the Turin Rheumatological Centre, in twenty (58 injections) the condition was acute, in fourteen (38 injections) the condition was chronic but without fixation of the joint, and in sixteen (58 injections) the joint was more or less "frozen". Hydrocortisone was injected, so far as possible, into the region of affected
tendons or of the subacromial bursa, but in a few intractable cases it was given intra-articularly. The usual dosage was 25 mg. (1 ml.), and an interval of 3 to 5 days was allowed between injections.

The best results were obtained in acute cases, where rapid relief from pain was experienced in all but one case, the final result being classified as "good" or "very good" in sixteen out of twenty. A similar degree of relief of pain was obtained in seven out of the fourteen chronic non-rigid cases, and in seven out of the sixteen cases with rigidity. Stiffness and immobility, however, appeared to be unaffected and required physical methods of treatment, which the relief of pain greatly facilitated. There was some evidence that calcification, when present, was more rapidly absorbed after treatment with hydrocortisone than is usually the case in spontaneous remissions. In the opinion of the authors, the radio-opaque appearances in such cases are due to subacromial bursitis, the fluid being rich in calcium salts. D. Preiskel.


Over a period of 18 months at the Hospital of the University of Pennsylvania, Philadelphia, 547 patients with rheumatic disease received injections of hydrocortisone into inflamed joints or bursae, the total number of injections being 3,757. Of the 547 patients, 249 had rheumatoid arthritis, 231 had osteo-arthritis, eighteen had gout, and 49 had various rheumatic conditions (details given).

The dose of hydrocortisone ranged from 5 to 50 mg. according to the size of the joint and the result obtained. Results were assessed both symptomatically and by the size and range of movement of the joint. Many of the patients with rheumatoid arthritis were receiving systemic treatment (cortisone or gold, or both) so that the results were difficult to assess, but it is considered that "satisfactory improvement" occurred in 85 per cent. of patients treated. Those with osteo-arthritis of the hip were noticeably resistant to treatment, possibly because of the technical difficulty of injection into this joint. Reactions, which occurred after 2-3 per cent. of the injections, included transient local exacerbation of inflammation, weakness of a limb, general malaise, urticaria, and in one case infection of the joint.

It is concluded that intra-articular injection of hydrocortisone is a useful adjuvant in the general treatment of rheumatoid arthritis, osteo-arthritis, gout, and various local rheumatic disorders. Kathleen M. Lawther.


The author describes the natural course of systemic lupus erythematosus in 83 patients seen at the Cleveland Clinic, Cleveland, Ohio, and assesses the results of treatment with cortisone or corticotrophin (steroid therapy) in 73. The series included only those cases in which the L.E. phenomenon was present. The author gives reasons for preferring the L.E.-plasma test to the L.E.-cell test; he considers that the former is as specific in the diagnosis of systemic lupus erythematosus as the Wassermann test is in the diagnosis of syphilis. He points out that before the introduction of the L.E.-plasma test a diagnosis of systemic lupus erythematosus was made only in typical, severe cases. Since then milder, atypical forms of the disease have been recognized, and when these are included in any series of cases the over-all prognosis is improved. A comparison of statistics of cases diagnosed by the L.E.-plasma test with those of cases diagnosed clinically is therefore invalid.

The course of lupus erythematosus in ten patients treated before steroid therapy was available is compared with that in 73 given cortisone or corticotrophin [details of the immediate and maintenance dosage are not given]. The author's criterion of effective therapy is the survival of those patients "considered to have iniminally fatal systemic lupus erythematosus". Only one of the ten untreated patients was alive 5 years after the onset of the severe phase; the remainder died one month to one year after onset. Of the treated patients, 44 were expected to die and steroid therapy is considered to have prevented death in thirty of these. A number of deaths occurred within a few days of the start of treatment. In four cases renal failure was progressive in spite of treatment. Of eleven patients given steroid therapy in 1949 and 1950, seven were alive in 1953. Not only was life prolonged by these drugs, but morbidity was reduced.

In the discussion which followed, the author discussed the false positive response to the L.E.-plasma test, which is sometimes noted in patients reacting to penicillin. Such patients were "very low-grade positive", only a small number of cells undergoing the characteristic changes. In systemic lupus erythematosus the reactions were always strongly positive. Nigel Compston.


The authors describe in some detail the effects of treatment with cortisone by mouth in five cases of pemphigus vulgaris, two of pemphigus erythematosus (Senear-Usher syndrome), and one of pemphigus foliaceus, giving the laboratory findings. Cortisone controlled or cleared the eruption in all cases except that of pemphigus foliaceus. Large doses (in one case 900 mg. a day) were given, and in one case of pemphigus vulgaris the cortisone was supplemented by heparin-sodium and later by nitrogen mustard. One patient, a man aged 43, whose skin had cleared completely with a dose of 600 mg. cortisone daily, later relapsed and died despite the resumption of treatment. ACTH (corticotrophin) produced no response in the three cases in which it was tried.

[Beyond the statement that "the patient must be followed indefinitely and supportive treatment with the drug given" no details of maintenance dosage are given.]

J. E. M. Wigley.
Treatment of Blood Disorders with ACTH and Cortisone.


The results of administration of ACTH or cortisone to 65 patients with haematological disorders are summarized. The daily dosage varied from 80 to 100 mg. ACTH and from 100 to 300 mg. cortisone. Most patients were treated for 2 to 3 weeks, the total dosage varying from 1,000 to 3,000 mg. ACTH and from 1,000 to 7,000 mg. cortisone. A "complete" response was defined as one in which the clinical condition of the patient and the haematological findings "returned approximately to normal", and a "partial" response as one in which "there was improvement of lesser extent".

Three out of ten patients suffering from idiopathic or secondary acquired haemolytic anaemia responded partially and five responded completely. The reaction to the antiglobulin (Coombs) test was negative in three patients, including the two who failed to respond. Treatment was given to 22 patients with purpura. Of fifteen with idiopathic thrombocytopenic purpura, ten responded favourably, but in five out of six patients with non-thrombocytopenic purpura treatment was ineffective. Of 24 patients with acute leukaemia of various types or reticulosis only five responded, the response being complete in two.

The effect of the hormones on other haematological disorders (nine cases) is briefly mentioned. The paper also contains the results of a follow-up examination of 88 patients given ACTH or cortisone in 1951 (Brit. med. J., 1952, 1, 1261; Abstracts of World Medicine, 1952, 12, 428).

It is concluded that the best results are likely to be obtained in cases of acquired haemolytic anaemia and of idiopathic thrombocytopenic purpura, but that as the response is usually temporary, treatment over many months may be necessary.

J. V. Dacie.


Studies of the metabolism of cortisone in slices of rat and human liver have confirmed the author’s previously published conclusion that para-aminobenzoic acid interferes with the inactivation of cortisone by liver tissue. It interferes markedly with the rapid reduction of the unsaturated conjugated system of the cortisone molecule, while permitting more rapid degradation of the side-chain.

W. S. C. Copeman.


The author, working at the Flensborg Children’s Hospital, Malmö, Sweden, has investigated the adrenocortical activity of newborn infants of diabetic mothers [with some interesting results].

In all, seven such infants were studied between the first and 14th day of life, and three infants of non-diabetic mothers acted as controls. Where possible, 24-hr specimens of urine were used for corticoid estimation, and up to six such estimations were performed in each case. The eosinopenic response to 5 mg. ACTH was also assessed in five of the cases, eosinophil counts being made before and 6 hrs after administration of corticotrophin. The urinary corticoids present were thought to represent 11-oxy cortisol steroids and 11-deoxy cortisol steroids, together with other as yet unrecognized corticoids.

The results, which were expressed in mg. per sq. metre of body surface, and in µg. per kg. body weight, showed that there was a significant increase in urinary corticoid excretion in six of the seven infants as compared with the control subjects and with the values for normal infants published by other workers. Four of the five infants were thought to show a significant eosinopenia following administration of ACTH. It was also shown that the urinary excretion of corticoids fell progressively from the initial high figure.

The author offers the intriguing suggestion that this increase in 11-oxy cortisol steroids offsets the hyperinsulin supposedly present in infants of diabetic mothers, as judged by the finding of pancreatic islet-cell hyperplasia. He also assumes that the high birth-weight, Cushing-like appearance, and oedema, all of which were lost rapidly in the first week, are due to the over-production of corticoids, which, however, tends to correct itself within the first week of life. He claims to have shown by electrocardiography that there is also evidence of hypokalaemia in such infants, and suggests that the administration of potassium salts might usefully be added to the usual treatment of these cases.

Had this appear to be an important paper, and further observations with larger numbers would be valuable. Figures for the eosinophil counts following administration of ACTH are rather borderline in all except two of the cases.

J. N. Harris-Jones.


An account of five cases treated with systemic cortisone, two of which had ocular complications for which local cortisone was given. Dramatic relief of pain, a shortened course of the disease, and absence of post-herpetic neuralgia are claimed.

H. E. Hobbs.


After a brief survey of the medical literature the authors give the results in 241 patients with various ocular diseases treated with local cortisone, usually by the subconjunctival route. The conclusions are:

(1) In affections of the eye with effusion or inflammation, the result is favourable.

(2) Local application is preferable to parenteral use because it does not provoke a general reaction and may be used in cases where general treatment is contra-
ABSTRACTS

indicated. Besides the absence of reaction, good tolerance and minimal doses are very important. It may also be used with out-patients.

(3) Subconjunctival injections are especially effective in affections of the anterior segment, whereas the introduction of cortisone to the anterior chamber should be reserved for serious cases of iridocyclitis. Retrobulbar injections and general treatment with cortisone or ACTH should be given in affections of the posterior segment of the eye as well as in cases where local use has not been satisfactory.

(4) Treatment should be initiated as early as possible and duration varies individually. Discontinuation of cortisone in some cases provokes a recurrence.

(5) Treatment with cortisone is symptomatic and auxiliary and should be combined with causal treatment in order to achieve a lasting effect and to avoid recurrence.

D. Lukić.


Topical applications of hydrocortisone have proved superior to cortisone and subconjunctivally it may be effective where cortisone has failed. These conclusions are based on an analysis of the treatment of 152 cases. The acetyl salt of hydrocortisone was inferior to the free-acid form when administered subconjunctivally. For lesions of the posterior segment of the eye an initial course of systemic therapy is followed by subconjunctival and then topical therapy.

S. J. H. Miller.


At the Medical Research Council Silicosis Treatment Centre, Stoke-on-Trent, twelve patients with chronic lung disease, all but two of whom had radiological signs of pneumoconiosis, were observed before, during, and after treatment with 100 mg. cortisone acetate daily by mouth for 14 days. Estimates of the maximum ventilatory capacity were made by measuring the expiration flow rate (E.F.R.); seven patients whose E.F.R. increased by more than 10 per cent. after inhalation of 1 : 1,000 adrenaline were considered to have "reversible bronchoconstriction".

Although eight of the twelve patients claimed subjective improvement of dyspnoea during and after cortisone therapy, the mean E.F.R. of the group both before and after adrenaline inhalation was unchanged. There was a slight but not significant fall in the mean erythrocyte sedimentation rate of the group at the end of the treatment. No radiological changes were seen and there was no evidence of activation of tuberculosis.

It is concluded that cortisone has no place in the treatment of bronchospasm in pneumoconiosis.

C. M. Fletcher.


An investigation was carried out at University College Hospital, London, to determine whether cortisone would influence an induced asthmatic attack. Asthma was induced by allowing the patient to inhale the appropriate allergen, and the intensity of the attack was judged by the time taken to induce it and the reduction in the vital capacity. Of eleven patients tested, five reacted "immediately"—that is, 2 to 10 min. after exposure; the remaining six were "late reactors"—that is, the asthmatic attack occurred 7 to 16 hrs after exposure. The patients were given cortisone, and when under its influence were exposed to double or treble the amount of allergen which had previously caused a mild attack of asthma. This exposure was repeated after the dose of cortisone was reduced and after administration of the drug ceased. It was found that after all three exposures to the allergen, the asthmatic attack in the immediate reactors was mild and transient; in the late reactors no asthmatic attack was produced. It is concluded that cortisone abolishes or modifies the violence of the reaction to an overdose of allergen, and prevents hypersensitization while permitting the development of hyposensitization. A. W. Frankland.


The author describes the results obtained at King's College Hospital, London, with ACTH in the treatment of four patients suffering from dystrophia myotonica. The myotonia was somewhat relieved, but in those cases in which wasting and dystrophy of the muscles were prominent features ACTH had little noticeable effect. This drug was preferred to cortisone because in previously reported cases the latter had proved of little value. The possible mode of action of ACTH on myotonia is discussed in relation to its effect on the potassium content of muscle.

J. B. Stanton.


The adsorption of an active drug on to a flocculent precipitate is a standard means of concentrating it and prolonging its period of effective action on injection. This technique has now been applied to corticotrophin (ACTH) since to obtain prolonged action from a single injection would be an advantage both clinically and economically, although concentration is not an important problem. These four papers deal with the adsorption product of corticotrophin and zinc phosphate.

In the experiments reported by Homan and others, the
combined product was shown to have an effect on the liver glycogen content of hypophysectomized rats greater than that of the same amount of ordinary corticotrophin in aqueous solution given in hourly doses over the same period (8 hours), while the reduction in weight of the thymus was equivalent to that produced by doses of the aqueous solution 10 to 32 times greater. Inactivation of ordinary corticotrophin by serum enzymes in vitro was considerable, but protection from enzymatic destruction and good stability was evident in the zinc suspensions in the presence of serum. A solution of 20 units corticotrophin and 1 to 2 mg. zinc chloride per ml. at pH 3.0 showed excellent stability on storage, and for clinical or biological use it was precipitated with trisodium phosphate and a final pH of 6.5 obtained by the addition of sodium hydroxide. Precipitation immediately before clinical use obviated crystallization in the flocculent suspension.

The effect of the combination of corticotrophin with zinc phosphate was compared with that of aqueous corticotrophin in six cases of rheumatoid arthritis by Greene and Vaughan-Morgan, the degree of amelioration of symptoms and increase in the urinary excretion of 17-ketosteroids (total neutral fraction) produced by each preparation being assessed. The effect of the combination of the symptoms was, in all but one case, better than that of ordinary corticotrophin, and was more lasting in four cases, the lack of superiority of the zinc preparation in the two other cases being attributed to an unusually prolonged effect of ordinary corticotrophin. The symptomatic effect of each injection of 20 units of the combination lasted 2 days or more, but better results were obtained by giving daily injections of 10-20 units. The 17-ketosteroid output was usually more than double that produced by ordinary corticotrophin in a similar dosage.

Ferriman and others compared the clinical effects of the corticotrophin-zinc-phosphate preparation and an “ethyl-oleate-beeswax preparation of corticotrophin” in seven cases of rheumatoid arthritis and one of ankylosing spondylitis. The latter preparation was never effective for more than 24 hrs, whereas the effect of the former lasted 24 to 48 hrs. Treatment with the zinc phosphate preparation resulted in a constant and persistent decrease in the eosinophil count and an increase in 17-ketosteroid excretion, whereas the effect of the ethyl oleate preparation was variable, although more constant than with ordinary corticotrophin.

Corticotrophin zinc phosphate was used by den Oudsten and others in 25 cases of rheumatoid arthritis. Although the therapeutic effect did not differ essentially from that obtained by frequent injections of ordinary corticotrophin, they point out that

"Corticotrophin zinc phosphate stimulates the adrenal gland for 24 to 48 hours or more after a single injection, as reflected by the eosinophil response and the urinary excretion of 17-ketosteroids, sodium, and potassium. A single injection of 20 I.U. of corticotrophin zinc phosphate has the same effect as four doses of 20 I.U. of ordinary corticotrophin injected 4-hrly”.

The action of zinc phosphate corticotrophin on the eosinophil count was found to set in as quickly as that of ordinary corticotrophin, but did not reach a maximum until about 8 hours after the injection and was much more prolonged. Harry Coke.


The authors describe three cases which were regarded as examples of the acute diffuse interstitial fibrosis of the lungs described in 1944 by Hamman and Rich. The duration of symptoms from onset to death was 51 months, 25 months, and 9 years respectively, and the histological changes, while resembling in every respect those described by Hamman and Rich only in the first case, seemed in the other two to represent a more chronic phase of the same process, consistent with the longer duration of symptoms. In none of the cases was any evidence relevant to the aetiology obtained, either during life or post mortem, and no response to antibiotics was observed. Cortisone or ACTH (corticotropin) was given in every case. In the first, which was in a relatively acute phase, there was remarkable radiological clearing of the lungs and symptomatic improvement during the administration of the hormones, but shortly after the gradual withdrawal of cortisone there was an acute exacerbation of dyspnoea and cyanosis, with a return of the original x-ray appearances, and despite large doses of cortisone and ACTH, the patient died within 24 hours of respiratory insufficiency. The second patient also died with severe respiratory difficulty shortly after the end of a 3-week course of cortisone which had produced no objective evidence of improvement. The third patient received moderate doses of ACTH for 27 days, and became very breathless after reduction of the dosage. In spite of reinstitution of treatment with large doses of ACTH together with cortisone, he died of respiratory failure.

J. G. Scadding.


The authors, after briefly reviewing previous reports of the effect of ACTH on mental function and in causing behavioural changes, describe an experiment carried out at the Walter Reed Army Medical Center, Washington, D.C., in which eleven unselected young male patients with acute hepatitis, five of whom were receiving ACTH as part of their treatment, were given psychological tests, before treatment began, between the 12th and 18th day (since this appeared to be a period when the effects of ACTH would be at their maximum), and after the end of treatment. The other six patients acted as controls. Each patient was interviewed by a psychiatrist before medication and two or three times per week thereafter, observations being made on the patient’s appearance, motor activity, mood, and behaviour. The total dose
Psychiatric Risk from Corticotrophin and Cortisone.


In order to test the thesis that cortisone and corticotrophin (ACTH) should not be given to patients with evidence of psychopathic personality, the authors studied twelve patients at the Maudsley Hospital, London, each of whom had a physical disease which might be relieved by these drugs and had also an unequivocal mental illness. Eleven of the patients had rheumatoid arthritis and one disseminated lupus erythematosus, and their psychiatric history indicated a severe degree of abnormality, including such conditions as obsessional neurosis, conversion hysteria, schizophrenia, and involutional depression.

After a control period of 6 weeks a placebo was given for 10 days, followed by corticotrophin or cortisone in increasing doses, starting with 40 to 60 mg. of the former and 100 mg. of the latter in 24 hours, until the maximum physical benefit had been obtained, the drug then being withdrawn slowly. The patients' physical condition responded as expected to the drug and relapsed during its withdrawal, while their mental condition improved concomitantly with the physical and relapsed at the same time; in fact the mental improvement seemed to be due to a psychological reaction (normal or hysterical) to the physical improvement rather than to a direct pharmacological effect. The findings of psychological tests before and during treatment provided no decisive evidence of cognitive or emotional changes.

It is concluded, therefore, "that predisposition to develop untoward mental symptoms under treatment with corticotrophin or cortisone cannot be assumed in patients with unstable neurotic personality or a history of mental illness". Oswald Savage.


The duration of the period of eosinopenia which follows burning was estimated to within \( \pm \frac{1}{2} \) day in 35 cases at the Birmingham Accident Hospital, and was plotted against the area of skin burned. The eosinopenia lasted only 1 to 2 days when less than 10 per cent. of the body area was burned, but up to 5 days when larger areas were burned. Eleven patients died during the period of eosinopenia and it is concluded that in these cases the adrenal cortex remained hyperactive until the time of death. In five of the seven other fatal cases there had been an initial period of eosinopenia of normal duration, and there was no other evidence of adrenal failure; in one of the remaining cases the period of eosinopenia had been unduly short.

In twelve out of fourteen patients tested, the response of the eosinophil count to ACTH was normal in the post-eosinopenic period, and the response to adrenaline was likewise normal in nine out of twelve patients tested. In neither of the two patients who responded abnormally to ACTH was the adrenocortical failure thus indicated considered to be serious, since one recovered and the other subsequently developed eosinopenia before death. Two of the three patients who responded abnormally to adrenaline responded normally to ACTH, indicating failure at the hypothalamic-pituitary level rather than adrenocortical failure. These patients were confused and irrational at the time of the abnormal response to adrenaline, the response becoming normal when mental recovery had taken place; it is therefore suggested that the mental disturbance and the lack of response to adrenaline were due to similar changes affecting the cerebral cortex and hypothalamus respectively.

It is recommended that severely burned patients should receive cortisone as soon as evidence of adrenocortical failure, in the form of either a premature return of the eosinophil count to normal or an abnormal eosinophil response to ACTH, is obtained. C. L. Cope.


Comparative Observations on the Therapeutic Effect and Tolerance of Cortisone and Hydrocortisone injected intra-articularly in Chronic Joint Disease. (Osservazioni comparative sull’azione terapeutica e sulla tolleranza del cortisone e dell’idrocortisone iniettati nel cavo articolare di artropatici cronici.) Robechi, A., and Dano, V. (1953). Reumatismo, 5, 368. 9 refs.


Other General Subjects


Sydenham is introduced as one who practised medicine first and foremost as an art—the “quiet art” of Virgil’s physician. To this end he set out to collect “as genuine and natural a description or history of all diseases as can be procured”. His attempt at a definition of disease is considered to show a greater insight into the essence of the matter than some current definitions of ill-health:

A disease, in my opinion, how prejudicial soever its causes may be to the body, is no more than a vigorous effort of nature to throw off the morbidic matter, and thus recover the patient.

Sydenham’s greatest claim to fame are his observations on the natural history of disease and his devotion to the cure of the patient. Born in 1624 of Puritan stock, he went to Oxford at the age of 18, but soon left to serve, first as a trooper and later as a captain, in the Parliamentary army. In 1647 he returned to Oxford to study medicine, being created Bachelor of Medicine by the Chancellor after only 6 months’ study—an irregular procedure even at that time. He later studied under Barbevraec at Montpellier, and after practising for some time in London became a Licentiate of the Royal College of Physicians. He was never elected to the Fellowship, but whether this was for political reasons or through personal animosity is not clear. He was highly regarded by many of his greatest contemporaries and was a personal friend of Robert Boyle and John Locke. Dr. Andrew Brown, a Scottish physician, and Thomas Dover, of Dover’s powder fame, were two of his medical disciples. Dover, who was Sydenham’s patient as well as pupil, has described how his smallpox was treated by a cooling regimen, with no fire, open windows, and few bedclothes, and twelve bottles of small beer every 24 hours.

Sydenham substituted faithful observation and accurate note-taking at the bedside for speculation and dogma. His achievement in medicine may be compared to that of his friend Locke in philosophy. Opinion among physicians was at first divided, but gradually turned in Sydenham’s favour, especially during the 18th century. On the Continent his reputation was greater than in his own country, and the renowned Hermann Boerhaave is said to have taken his hat off whenever he mentioned the name of the “English Hippocrates”. His achievements included the introduction of a tincture of opium, the cooling treatment of smallpox, and the use of Peruvian bark in quaran agues. He described the rheumatic type of chorea, recorded his own sufferings from gout, and left classic descriptions of smallpox, measles, and scarlet fever. His abiding fame rests chiefly on his “natural history” method in the study of disease—especially epidemic disease—and his advocacy of practical bedside medicine.

The study of Sydenham and his work calls to mind the dual nature of medicine. While his great contemporary Harvey stands out primarily as a man of science, Sydenham must be regarded as one who practised the art of medicine. This is not to suggest that he made no use of scientific methods, but it explains how his devotion to immediate needs meant that much that was best in him died with him. He has been well described by Major as “the greatest representative of the practical medicine of practical England”.

W. J. Bishop.

