obtained from the bottom, middle, and top of the bulb. The table shows the scatter of cells to have been even throughout the pipette in every case, both in chambers flooded from pipettes immediately examined and in those which had been allowed to stand for four hours.

That these clumps of cells could not be broken up by prolonged shaking was proved in four cases by shaking a duplicate pipette for ten minutes, the microscopical appearances remaining unchanged. The homogeneity of the counts obtained from 12 chambers flooded within 30 minutes of collection and the absence of clumping in all counts thus examined gave sufficient proof that clumping was not due to insufficient mixing of blood and diluting fluid at collection. To check this, four duplicate pipettes were shaken for two minutes immediately after collection and again after standing for four hours. Clumps still appeared in the majority of chambers examined.

In an attempt to prevent this error, due possibly to the normal clotting of the blood within the pipette, heparin was added to the diluting fluid in a concentration of one unit per millilitre. The table shows that this addition completely eliminated the error, the counts so obtained on blood which had stood for four hours being closely comparable to those obtained on immediate counting. Nor were clumps visible microscopically in the preparations.

Such clumping does not follow the standing of pipettes when Randolph's fluid is used. Though the addition of heparin eliminates the error when using Pilot's fluid, it is unlikely, therefore, that a clotting mechanism alone is responsible. The answer possibly exists in the pH difference between the two stains. The pH of Randolph's fluid is 7.4, that of Pilot's fluid 10.55. The alkaline pH of the latter would allow of possible partial denaturing of the blood proteins, fibrin being the first partially to precipitate with pH variation. The use of buffer solutions other than sodium carbonate to produce a pH of 10.55 brought about similar clumping of the cells on standing.

Two further crude tests have been employed to establish that the stroma which binds the cells on standing is fibrin. First, streptokinase (Cathie, 1949) has been added to the diluting fluid in a concentration of approximately four units per millilitre. This experiment has been done in six duplicate tests. The counts obtained after a delay of four hours when using such a modified stain are, within experimental error, those obtained following the use of heparin and those resulting on immediate counting of unmodified fluid preparations. Secondly, 1 ml. of blood has been added to 9 ml. of diluting fluid and the mixture allowed to stand for four hours. Flooded over a white surface, the fluid shows macroscopic clots which, when gathered from several specimens and sectioned, appear to consist of a stroma of material staining as fibrin enmeshing eosinophils and other leucocytes. A more detailed investigation of this problem is proceeding.

Summary

Attention is drawn to Pilot's fluid for the enumeration of eosinophils. Counting is much easier and quicker than with Randolph's fluid, while the disadvantage of Rud's fluid is also overcome.

A source of error in the use of the fluid is the clumping of leucocytes on standing. This may be eliminated by the addition of heparin to the fluid in the concentration of one

unit per millilitre. There is some evidence that this clumping is due to the formation of fibrin within the pipette.

We are indebted to Dr. I. A. B. Cathie, clinical pathologist, in whose laboratory the investigation was carried out, for much helpful advice and criticism.

REFERENCES

- Cathie, I. A. B. (1949). *J. clin. Path.*, **2**, 73.
 Dunger, R. (1910). *Münch. med. Wschr.*, **57**, 1942.
 Pilot, M. L. (1950). *Amer. J. clin. Path.*, **20**, 870.
 Randolph, T. G. (1944). *J. Allergy*, **15**, 89.
 Rud, F. (1947). *Acta psychiat., Kbh.*, Suppl., **40**, 1.
 Sanders, C., Parry, K. C., Bennett, A. E., and Geisow, J. C. H. (1950). *J. clin. Path.*, **3**, 367.

ADDISON'S DISEASE WITH ASSOCIATED POLYARTHRITIS AN AETIOLOGICAL STUDY OF THE ARTHRITIS SYNDROME

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In view of the therapeutic response to cortisone (compound E) in Addison's disease and in rheumatic diseases some correlation between these two disorders might be expected. In the literature, however, the association of the two diseases is notably infrequent. Bauer *et al.* (1951) could find no record of active rheumatoid arthritis in association with untreated Addison's disease.

Addison's disease is undoubtedly an endocrine disorder, but the possibility that the rheumatic diseases are fundamentally due to an endocrine disorder has not been demonstrable by clinical, laboratory, or pathological investigation. Some authors (Dejean, 1947; de Gennes *et al.*, 1947; Laroche, 1947a, 1947b) have reported Addison's disease with rheumatic joint lesions in cases under treatment with deoxycortone acetate (D.C.A.).

Selye (1949) noted that rats treated with large doses of D.C.A. often developed joint lesions which had histological changes characteristic of rheumatic arthritis and peri-arthritis. These lesions occurred in only a percentage of the rats, although some rheumatic manifestations were present in all. In some rats in which the arthritis appeared within a few weeks it was noted that the arthritic lesions cleared in spite of continued administration of D.C.A. Rarely, the arthritic lesions progressed to lesions comparable to those seen in rheumatoid arthritis. Selye found that if rats were adrenalectomized before the administration of D.C.A. they were more susceptible to these toxic effects of D.C.A. on the joints. He observed that cortisone relieved the arthritis. He stated that the significant aetiological factor in the genesis of the rheumatic joint lesions is an imbalance between the mineralo-corticoids of the adrenal cortex and the gluco-corticoids.

The following case is presented on account of the current interest in the aetiology of arthritic lesions.

Case Report

A farmer aged 58 had had for 15 years recurrent attacks of polyarthritis affecting his fingers, carpus, wrists, elbows, shoulders, and occasionally his knees. In 1939 he developed lobar pneumonia and empyema, which necessitated a thoracotomy and drainage. A chronic discharging sinus resulted, and this persisted for 10 years. In 1949 Mr. Stanley Wilson performed a lobectomy, and the sinus was successfully closed. In 1949 he developed an attack of polyarthritis affecting the fingers and wrists and other joints to a less extent. Dr. Raymond Kirk diagnosed rheumatoid arthritis. After a short course of gold therapy the arthritic changes subsided.

In April, 1950, he developed pain and swelling in his left hip, and a fluctuant swelling, from which pus was aspirated, developed over the great trochanter. A positive guinea-pig test proved this to be tuberculous. About this time he became excessively weak, his appetite failed, and he lost weight steadily. He developed a notable craving for salt, and at intervals was nauseated and had bouts of vomiting. Addison's disease was diagnosed in February, 1951, and treatment with 10 mg. of D.C.A. intramuscularly and 6 g. of sodium chloride daily was started 10 days before admission to hospital.

On admission to Dunedin Hospital on March 7 he was wasted and weak. His head hair was soft and fine and his body hair was scanty. Axillary and pubic hair was of normal distribution but somewhat scanty. There was generalized increase of pigmentation, most pronounced at the pressure areas and in the skin creases. The nipples and scrotum showed marked pigmentation. A few patches of pigmentation were present in the mucous membranes of the mouth. On the arms there were some small pin-point areas where pigmentation had been lost. The respiratory system was normal. The apex beat was in the fifth left interspace $4\frac{1}{2}$ in. (12.1 cm.) from the midline. The sounds were regular and of moderate intensity; the rate was 100. There was a presystolic gallop rhythm. The blood pressure was 118/64. The joints were normal.

Investigations.—The urine was normal. Radiography showed the chest to be clear, and a plain radiograph of the abdomen showed no adrenal calcification. Gastric analysis revealed a hypochlorhydria. Blood count: red cells, 3,430,000; haemoglobin, 64%; white cells, 5,900 (11% eosinophils). The serum sodium was 288 mg. per 100 ml. and the serum potassium 19 mg. per 100 ml. The Congo red test for amyloid disease was normal.

Treatment

At the time of admission no cortisone was available and treatment was continued with 10 mg. of D.C.A. and 6 g. of salt daily. Five days after admission he developed arthritic changes of the carpo-metacarpal joint of the forefinger on the left hand and the left elbow. The joints were swollen and tender, and movement was restricted by pain. The following day diarrhoea began and his fluid output fell to 240 ml. There was a deterioration in his general condition. The blood pressure fell to 100/68. The heart was fibrillating. (E.C.G. report: There is an irregular rhythm, possibly auricular fibrillation. There is a suggestion in Lead V₂ of a nodal type of rhythm. The rate is 70 a minute. Standard leads show low-voltage T waves throughout. Chest leads: there is counter-clockwise rotation, transition point being between V₁ and V₂. The T wave is flattened but upright. It is of very low voltage in V₅. The shape of the QRS is not abnormal. The Q-T time looks prolonged. Unipolar limb leads show that the heart tends to be horizontal. There is a low voltage throughout. T waves are indeterminate.) In the next three days there was further deterioration. The urinary output fell to 100 ml. and the blood pressure could not be recorded. The patient became confused, disorientated, and incontinent, and was in a state of toxic delirium. The 17-ketosteroids were 1.3 mg., the serum sodium was 288 mg. per 100 ml., and the serum potassium rose to 24 mg. per 100 ml. The serum uric acid was 2.8 mg. per 100 ml.

Treatment with cortisone (Merck) was begun on March 18, with 300 mg. intramuscularly followed by 100 mg. daily. The D.C.A. was increased to 20 mg. daily and the salt maintained at 6 g. daily. He was given digitalis from the onset of fibrillation.

Thirty-six hours after cortisone was begun there was a striking improvement in his general condition. The toxic delirium cleared; he became continent and the urinary output rose; and his heart sounds improved. He improved for the next 19 days while cortisone treatment was maintained—100 mg. for eight days and 50 mg. thereafter. After 10 days the D.C.A. was decreased to 10 mg. daily.

Five days after the onset of treatment with cortisone the joint swellings had subsided completely. The eosinophil count fell to zero. Screening at the conclusion of cortisone therapy showed a considerable increase in the size of the heart. The electrocardiogram showed left ventricular preponderance. The serum sodium rose to 306 mg. per 100 ml., the uric acid was 2.7 mg. per 100 ml., and serum potassium fell to 18 mg. per 100 ml.

When supplies of cortisone failed, D.C.A. by injection was discontinued and 100 mg. was implanted into the abdominal wall. This small dose was chosen on account of observed cardiac enlargement. The salt was reduced to 1 g. daily. A week later the patient began to show signs of further deterioration. The blood pressure fell, the pulse increased, and he complained of swelling, pain, and tenderness of the second left metacarpo-phalangeal joint and the left medio-carpal joint.

Cortisone became available again, and 100 mg. was injected daily. Two days later there was an improvement in his general condition and the arthritic changes subsided.

A further trial was carried out: cortisone was discontinued and D.C.A. was recommenced (10 mg. daily), and salt was increased to 8 g. daily. Three days later he complained of pain in his right shoulder. On examination the joint appeared normal. The following day the right elbow became swollen, tender, and reddened, and in the next two days the right medio-carpal joint and both elbow-joints became swollen, hot, and tender. A day later the small joints of the right middle finger swelled and most of the finger-joints of the left hand were involved. On the same day there was a general deterioration with a fall in blood pressure and tachycardia, and the serum sodium fell to 260 mg. per 100 ml.

Cortisone was recommenced—300 mg. daily for two days, and then 100 mg. daily. Within three days all arthritic changes had subsided and full range of movement was restored in the affected joints. He was transferred to a convalescent hospital for three weeks on a maintenance dose of cortisone, 50 mg. daily, and salt, 4 g. daily. The improvement was maintained and his weight increased by 11 lb. (5 kg.) in three weeks.

A week later cortisone and salt were discontinued again, and D.C.A. 10 mg., and promethazine hydrochloride ("phenegan") 1 mg., an antihistaminic, were given daily. Within five days the arthritic lesions recurred and were again controlled when cortisone, 100 mg. daily, was given.

Discussion

This patient presented a picture of Addison's disease with associated polyarthritis. After the diagnosis of Addison's disease, salt and D.C.A. therapy was begun, and soon after admission to hospital six weeks later there was painful arthritis involving the carpus joints of both hands. When cortisone was added to the therapeutic regime the arthritis promptly settled. When cortisone supplies failed and salt and D.C.A. were increased, arthritis returned in a more severe form, affecting interphalangeal joints of the hands, the carpus joints, and both elbow-joints. Again on resuming treatment with cortisone the arthritic lesion cleared promptly within four or five days.

Selye (1949) reported a technique for the production of an acute arthritis and peri-arthritis by the injection of formaldehyde into the vicinity of joints. If large doses of formaldehyde were administered the acute stage was followed by a very prolonged chronic arthritis and peri-arthritis characterized by moderate oedema and pronounced connective-tissue proliferation. This chronic arthritic condition continued to proliferate for weeks after the initial injection of irritant. He also found that this arthritis was aggravated by a preliminary treatment with D.C.A. or crude anterior pituitary extract, and it could be almost completely inhibited by cortisone or adrenocorticotrophic hormone (A.C.T.H.), suggesting an antagonistic relationship between D.C.A. and crude anterior pituitary preparations on the one hand and cortisone and A.C.T.H. on the other hand.

In a recent paper Selye (1951) further reports that with electrophoretically pure somatotrophic hormone (S.T.H.) (growth hormone) he can increase the sensitivity of the rat to the production of experimental arthritis. He concludes that the S.T.H. appears to play a part equally as important as A.C.T.H. The former is responsible for the activity of the mineralo-corticoids which produce arthritic changes, whereas the latter regulates the secretion of the gluco-corticoids which protect against the formation of arthritis.

In discussing Selye's findings the *British Medical Journal* (1951) suggested that the effects obtained may be those of a non-specific allergic reaction to foreign substances. Selye (1950) has shown that naturally occurring desoxocortisone (Reichstein's compound "S") also causes the lesions, making this explanation very unlikely; and he finds the suggestion of allergy difficult to reconcile with the fact that among a group of adrenal steroids tested only those with mineralo-corticoid activity exert such an allergic action, while among a group of proteins tested only pituitary extracts with somatotrophic hormone activity elicit comparable changes under experimental conditions.

Furthermore, if considerations are limited to cattle pituitary proteins it is found that A.C.T.H. inhibits while S.T.H. enhances the development of these collagen lesions. Adrenalectomy prevents this detrimental effect of S.T.H.-containing pituitary extracts. This also argues against their allergic nature, since adrenalectomy generally sensitizes the rat to allergic responses. It is also known that salt supplements the unilateral nephrectomy in sensitizing the organism to the actions of the mineralo-corticoids and of S.T.H.-containing pituitary extracts. Neither of these factors influences the course of allergic reactions. In our patient it was notable that the administration of an antihistaminic (promethazine hydrochloride) with D.C.A. failed to prevent the development of the polyarthritis in the absence of cortisone. Also it seems unlikely that D.C.A., which is so closely allied to a naturally occurring substance that is not a protein, should act in this manner. Furthermore, if this response of the joints to D.C.A. and salt was an allergic reaction, it would be reasonable to expect it to occur promptly within 24 hours or less, whereas it has appeared three to five days after the D.C.A. and salt had been given.

Just as a rat treated with formaldehyde in the vicinity of a joint is predisposed to develop arthritis, it is apparent, from the long history of recurrent rheumatic joint lesions, that our patient was predisposed to develop arthritic lesions. The salt and D.C.A. acted

as an aggravating factor and precipitated an attack of rheumatic joint disease. It has been stressed that the clinical association of Addison's disease and rheumatic joint lesions is notably infrequent, and this in spite of the free administration of D.C.A. and salt to many patients with Addison's disease.

On this account we cannot subscribe in detail to Selye's contention, but suggest that, provided there is a pre-existing tendency in an individual to develop rheumatic joint lesions, a significant aggravating factor in the pathogenesis of these lesions is an imbalance between the mineralo-corticoids and the gluco-corticoids of the adrenals.

Summary

A case of Addison's disease and recurrent polyarthritis is described.

Treatment with D.C.A. and salt appeared to precipitate an attack of polyarthritis with swelling and pain. Cortisone readily controlled this arthritis.

Also, an antihistaminic given with D.C.A. failed to protect the patient from the polyarthritis, which was again controlled with cortisone.

The pathogenesis of rheumatic joint lesions is discussed. It is concluded that, if there is a pre-existing tendency to develop rheumatic joint lesions, a significant aggravating factor in the pathogenesis of the joint lesions is an imbalance between the mineralo-corticoids and the gluco-corticoids.

REFERENCES

- Bauer, W., Clark, W. S., and Dienes, L. (1951). *Practitioner*, **166**, 5.
British Medical Journal, 1951, **1**, 285.
 de Gennes, L., Mahoudeau, D., and Bricaire, H. (1947). *Bull. Soc. méd. Hôp. Paris*, **63**, 532.
 Dejean, C. (1947). *Pr. méd.*, **55**, 439.
 Laroche, G. (1947a). *Ibid.*, **55**, 481.
 — (1947b). *Bull. Soc. méd. Hôp. Paris*, **63**, 616.
 Selye, H. (1949). *British Medical Journal*, **2**, 1129.
 — (1950). *Ibid.*, **1**, 203.
 — (1951). *Ibid.*, **1**, 263.

PENICILLIN TREATMENT OF ACUTE MASTOIDITIS IN CHILDREN

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In July, 1949, I presented to the International Congress of Otolaryngology a report on 50 cases of acute mastoiditis in children treated with penicillin injections between July, 1946, and July, 1948. So far as is possible these cases have been followed up, and it would now seem appropriate to discuss them, note what was attempted, and assess progress up to the time of writing.

Diagnosis

In 1946 it was decided to attempt the treatment of obvious acute mastoiditis or abscess by penicillin injection alone. The selected cases were to be those admitted to hospital as emergencies under the diagnosis of acute mastoid abscess, because during the course of an acute suppurative otitis media a post-aural inflammatory swelling had appeared. It was most important that all cases should be true acute conditions and not post-aural abscess consequent upon exacerbation of chronic tympano-mastoiditis.