MILD CUSHING'S SYNDROME DUE TO ASPIRIN

BY

J. B. COCHRAN, M.B., B.Sc., F.R.F.P.S., M.R.C.P.

R. D. WATSON, B.Sc.

AND

J. REID, M.D., M.R.C.P.

(From the Clinical Chemotherapeutic Research Unit of the Medical Research Council, in the Gardiner Institute of Medicine, University of Glasgow)

Since Hench, Kendall, Slocumb, and Polley (1949) first reported the results of treating rheumatoid arthritis with 17-hydroxy-11-dehydrocorticosterone ("compound E," or cortisone) disturbing side-effects have been observed following prolonged treatment which suggest the development of a mild Cushing's syndrome. The effects which have been recorded are rounding of the facial contours, hirsutism, acne, dorsal fat pad, glycosuria and diminished glucose tolerance, sodium retention leading to oedema, alkalosis, hypertension, and alteration of psyche. Hench and his colleagues (1950) state that there is no characteristic pattern for the development of side-effects. In their series of 23 rheumatoid patients treated with cortisone or A.C.T.H. the commonest side-effects were mild and occurred in eight patients. The effects noted in these cases were "mild acne, mild hirsutism, rounding of the face, and mild irritability." According to Baehr and Soffer (1950) side-effects occur more often during the treatment of acute conditions such as disseminated lupus erythematosus than in rheumatoid arthritis.

The metabolic effects of cortisone as summarized by Carlisle (1950) are retention of sodium and water early in the course of treatment, especially on high dosage, followed by spontaneous diuresis on continued administration of the hormone or after its discontinuation. High dosage has caused increased excretion of potassium with metabolic alkalosis in some cases, and the continued administration of large doses usually produces a negative nitrogen balance. Carlisle, in describing the clinical effects of cortisone in acute rheumatic fever, states that, in addition to the beneficial effects on arthritis, pyrexia is abolished in one to four and a half days, tachycardia in three and a half to five days, and in some cases a bradycardia follows; the E.S.R. becomes normal within 12 to 18 days; haemoglobin value increases by as much as 2.4 g. within three weeks in patients in whom the pretreatment levels are low; and in almost every instance cortisone causes a slight increase in the values for serum albumin and a reduction in the values for serum globulin.

The following report is of a patient suffering from a third attack of acute rheumatic fever who under treatment with aspirin developed signs of a mild Cushing's syndrome, which disappeared as the acute attack subsided and aspirin dosage was reduced. The clinical and metabolic effects observed during aspirin therapy resemble closely those attributed to cortisone.

Case Report

A girl aged 13 was admitted to hospital on September 29, 1950, suffering from an acute attack of rheumatic fever of one week's duration. This was her third attack, and the clinical findings on admission included severe general prostration, pyrexia (104° F.—40° C.), tachycardia (120 a minute), rapid

respiratory rate (44 a minute), a dry coated tongue, and a dry warm skin. The heart was grossly enlarged, the apex beat being distinctly palpable on the anterior axillary line. Apical systolic and diastolic murmurs were present and the veins of the neck were overfilled, though there was no peripheral oedema or hepatic enlargement. The lower lobe of the left lung was collapsed. An electrocardiogram suggested pericarditis, and a portable x-ray film of the chest showed the cardiac outline of mitral valvular disease. The collapse of the left lower lobe was probably due to pericardial effusion and cardiac dilatation. The other clinical features were acute arthritis of the joints of the second and third fingers of both hands, both wrists, and the right elbow.

The patient was given a standard diet, and on September 30 administration of a dihydroxybenzoate in doses of 1 g. daily was started, and was continued for four days. This substance is at present under test, and will be reported on later. The acute arthritis disappeared within 24 hours, the temperature and rapid respiratory rates began to fall, but there was only a slight drop in the pulse rate. Improvement was thought to be too slow, so it was decided to change to aspirin treatment on October 4. Aspirin was given in doses of 1 g. five times daily, and the temperature, pulse, and respiratory rates continued to fall.

On the second day of aspirin treatment the face appeared to have become rounded and it looked "puffy," although there was no pitting on pressure. During the next 10 days the pulse and respiratory rates slowly settled and the temperature remained about 98–99° F. (36.7–37.2° C.). On October 17, 13 days after the start of aspirin treatment, acne was observed on the front of the chest and along the hair margin of the forehead. It later spread to the shoulders and back. A specimen of urine was found at this time to reduce Benedict's solution, producing a yellowish deposit. On account of a possible salicylate fallacy, a fermentation test with controls was set up; this showed the abnormality to be a reducing sugar. It was noticed that for some days the patient had been extremely morose, would not respond to questions, and never smiled, and this demeanour seemed to be out of proportion to the malaise of her illness. She continued to improve under aspirin therapy, and on October 19 the dosage was reduced to 1 g. thrice daily. Next day the face looked a little less "puffy," and from this point cheek measurements, using special callipers, were recorded. By November 2 each cheek had shown a reduction in thickness of 1.5 mm. Aspirin dosage was further reduced to 1 g. twice daily on October 23, and to 1 g. daily on October 28 for a further four days. The rounding of the facial contours and acne gradually disappeared and she lost her surly demeanour.

A glucose tolerance test was carried out on the day after a reducing sugar was found in the urine. The blood sugar (Folin and Wu) showed a high fasting level (163 mg. per 100 ml.), rising during the following two hours well above the normal renal threshold, and the urine contained glucose. A sudden fall to levels below 130 mg. occurred at two and a half and three hours. The next day the fasting level was 147 mg. Further tests showed that glucose tolerance returned to normal as aspirin dosage was reduced (Fig. 1).

The effects of treatment on the E.S.R. (Westergren), haemoglobin level, temperature, pulse, and respiratory rates are shown in Fig. 2. The temperature reached normal limits within two days of beginning aspirin therapy, but the pulse rate fell more slowly and reached normal on the twelfth day. A few days later the patient developed a bradycardia, which lasted six days. The E.S.R. fell from an initial level of 82 mm. to 12 mm. an hour within three weeks of beginning aspirin treatment. Increase in haemoglobin value by 2.8 g. occurred within four weeks.

The results of fluid, chloride, and nitrogen balance studies are shown in Fig. 3. During the first 10 days of aspirin treatment water and chloride were retained and the output of nitrogen greatly exceeded intake. During the next 15 days the volume of urine relative to the fluid intake progressively increased, and this was accompanied by an increased output of chloride and a steady diminution in nitrogen output.

FIG. 1.—Glucose-tolerance curves after the ingestion of 50 g. of glucose following a 12-hour fast. Curve A was obtained at the height of aspirin therapy; curves B and C were obtained later, when aspirin was withdrawn.

FIG. 3.—Effect of therapy on fluid, chloride, and nitrogen balance.

During the course of treatment the albumin-globulin ratio fell to normal from its original reversed state. Serum albumin rose by 2.3 g. and globulin fell by 1.7 g. Plasma fibrinogen fell from its original high level of 0.77 g.% to 0.42 g.%.

Ketosteroid excretion (Tompsett and Oastler, 1946) was estimated daily from October 17 to 30 and showed no significant alteration. The daily output varied between 5.4 and 8.8 mg.

Discussion

The clinical and metabolic effects of aspirin in this patient are identical with those previously reported (Reid, Watson, and Sproull, 1950). The effect of aspirin on pyrexia, tachycardia, E.S.R., and haemoglobin level compares favourably with that reported for cortisone. The two substances have the same effect on fluid, chloride, and nitrogen balance and on plasma protein. The similarity is further strengthened by the development under aspirin therapy of side-effects suggesting a mild Cushing's syndrome.

If aspirin and cortisone have a similar action certain important considerations arise. Aspirin may stimulate the adrenal cortex to produce cortisone or may act in this way via the pituitary and the secretion of A.C.T.H.; or the two substances may have an identical peripheral action. Aspirin and cortisone appear to differ in one respect. The former produces a respiratory alkalosis, while the latter causes a fixed base alkalosis. This discrepancy may be explained by the great difference in therapeutic dosage of the two substances. The comparatively large doses of salicylate lead to accumulation of the drug in the plasma, displacement of equivalent amounts of bicarbonate, and a raised plasma pH (Reid, Watson, and Sproull, 1950). As plasma pH depends on the ratio $\text{H}_2\text{CO}_3 : \text{NaHCO}_3$, any reduction in bicarbonate must be accompanied by an equivalent reduction in the concentrations of plasma H_2CO_3 . This may be achieved by increasing alveolar volume, which lowers alveolar CO_2 concentration and

FIG. 2.—Effect of therapy on haemoglobin, E.S.R., temperature, pulse, and respiratory rates. The times of appearance of the side-effects suggesting Cushing's syndrome are indicated.

therefore plasma H_2CO_3 . The clinical counterpart of this physiological adjustment is the slow deep breathing on salicylate administration.

It is realized that a single case has been cited as evidence of a possible common action of aspirin and cortisone, but on examination of our records of previous cases of acute rheumatism treated with sodium salicylate we find that frequent reference is made to puffiness of the face and acne-like lesions on the face, front of chest, and back. In fact, puffiness of the face may be observed in almost every patient receiving full therapeutic doses of salicylate, and it tends to be most pronounced in children. Most of these patients also had a reducing substance in the urine which was assumed to be a salicylate fallacy. However, addition of salicylic acid, sodium salicylate, and aspirin to normal urine in concentrations greater than we have ever encountered in the urine of patients under treatment failed to show any reduction of Benedict's solution. This does not exclude the presence of reducing substances other than glucose, but it may well be that the reductions previously observed were partly if not wholly due to glucose. These retrospective observations suggest that the development of mild Cushing's syndrome during intensive salicylate treatment is not uncommon, but there are many points requiring further investigation before any final conclusion may be drawn. Nevertheless, it is thought that this initial report is justified in view of the significance of the findings.

Summary

The clinical and metabolic effects of aspirin in the treatment of acute rheumatism resemble closely those attributed to cortisone.

A case is presented, and others referred to, in which the similarity in action of the two substances is further strengthened by the development under aspirin treatment of side-effects suggesting a mild Cushing's syndrome.

The effects observed were rounding of the facial contours, acne, diminished glucose tolerance, glycosuria, and alteration of the mental state.

Some important considerations arising out of this conception are discussed.

We thank Professor J. W. McNee for his advice and generous help in providing facilities for this work. We are also indebted to Mr. S. L. Rae for the ketosteroid estimations.

REFERENCES

- Baehr, G., and Soffer, L. J. (1950). *Bull. N.Y. Acad. Med.*, **26**, 229.
 Carlisle, J. M. (1950). *British Medical Journal*, **2**, 590.
 Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1949). *Proc. Mayo Clin.*, **24**, 181.
 ——— (1950). *Arch. intern. Med.*, **85**, 545.
 Reid, J., Watson, R. D., and Sproull, D. H. (1950). *Quart. J. Med.*, **19**, 1.
 Tompsett, S. L., and Oastler, E. G. (1946). *Glasg. med. J.*, **27**, 281.

The British Standards Institution has issued a British Standard for one-mark bulb pipettes. Sixteen sizes of pipette from 1 ml. to 100 ml. capacity are specified, being those most in demand for general laboratory use. Full dimensions are given, but, in accordance with current practice in British Standards for laboratory glassware, only the essential ones are listed as mandatory, the remainder being given for the guidance of manufacturers. Standard methods are included for the determination of capacity and delivery time, and tolerances listed for both. An appendix gives the sizes of glass tubing recommended for the manufacture of these pipettes. Copies of this standard may be obtained from the British Standards Institution, Sales Department, 24, Victoria Street, London, S.W.1 (2s. post free). The Institution has also issued standards for hospital beds and other hospital equipment, and for paper boxes for pills, creams, powders, pastes, etc.

EVALUATION OF TREATMENT IN INTERMITTENT CLAUDICATION*

BY

J. T. SHEPHERD, M.B., M.Ch.

Lecturer in Physiology, Queen's University of Belfast

Arteriosclerosis is by far the commonest cause of intermittent claudication, and numerous drugs and operations have been advocated for the treatment of this condition. Any effective treatment must increase the distance a patient can walk, either by increasing the blood flow to the affected muscles or by reducing the pain which occurs on exercise.

Direct measurement of the distance a patient can walk is the common method of assessing treatment. This has two disadvantages. First, if improvement does occur it is impossible to say whether this is due to an increased blood flow to the muscles or to a pain-relieving action of the drug. Secondly, it does not allow the limbs to be tested separately. Often both legs are affected by the disease, but the earlier onset of pain in the more severely affected one may stop the patient walking before pain is felt on the other side.

An alternative method for evaluating treatment is described which does not suffer from these disadvantages.

Methods

The method employs an ergograph to determine the amount of work a patient can perform and a venous occlusion plethysmograph to enable the blood flow through the calf to be measured after the exercise.

The ergograph has already been briefly described (Shepherd, 1950). The patient, by depressing a foot-board on plantar flexion, raises a weight. The foot-board is so arranged that the axis of its movement passes through the ankle-joint (Goetz, 1942) and, as the leg is kept horizontal, with the knee flexed through an angle of about 60 degrees, the posterior calf muscles perform most of the work.

On the return stroke, as the ankle is dorsiflexed, the speed of the falling weight is controlled by a brake (Fig. 1). Alternate contraction and relaxation of the muscles is therefore possible, the posterior calf muscles being relaxed on dorsiflexion instead of having to resist the descent of the weight. This is important, because it leads to a large difference between the amount of work that can be done by the normal and the arteriosclerotic subject. The normal adult male of whatever build can make 500 contractions at a rate of 24 a minute and show no sign of fatigue or pain at the end. The number of contractions that can be made by arteriosclerotics with symptoms of claudication varies according to the severity of the disease, but even mild cases are generally forced to stop by pain and fatigue in the affected muscles before they have completed 200 contractions. The ergograph could also be adapted for testing the extensor muscles of the leg so that work is performed on dorsiflexion only. In practice this has never been done, as in all our patients pain on exercise was limited to the posterior calf muscles. The movement of the foot-board is transmitted to an indicator. A mark is placed on a scale behind the indicator, and by pushing to this mark the foot-board moves through an angle of 33 degrees and the subject lifts a 5.5-kg. weight a distance of 26 cm. By arranging

*This work was carried out during tenure of a British Medical Association scholarship.