pre-pyloric carcinomata frequently undergo peptic ulceration and may then present with the histological features of so-called "ulcer-cancer."

We believe that the second possibility is inherently more likely. But, in any event, from a practical standpoint the main conclusion is unaffected by one's choice between these two possibilities. It is that pre-pyloric ulcers are commonly malignant and should be resected.

Summary

Among 375 patients with gastric carcinoma treated in the Radcliffe Infirmary there were 26 with some evidence that the neoplasm might have arisen in a simple ulcer.

There was good clinical evidence of chronic simple ulcer in only half the patients.

The site of the neoplasm for the group of 26 patients conformed with the distribution of carcinoma of the stomach and not with that of simple gastric ulcer.

In three cases the carcinoma had apparently arisen at a site different from that of a pre-existing simple ulcer.

We believe that most of these cases were examples of ulcerating carcinoma. In any event, the majority were pre-pyloric, and it is evident that pre-pyloric ulcers should be deemed malignant and treated by surgical resection.

We wish to thank the physicians and surgeons of the Radcliffe Infirmary for permission to make the study out of which the present article arises.

REFERENCES

- Brown, R. C. (1930). *J. Amer. med. Ass.*, **95**, 1144.
 Cabot, H., and Adie, G. C. (1925). *Ann. Surg.*, **82**, 86.
 Dible, J. H. (1924). *Brit. J. Surg.*, **12**, 666.
 Ewing, J. (1918). *Ann. Surg.*, **67**, 715.
 Moynihan, B. G. A. (1906). *British Medical Journal*, **1**, 370.
 Newcomb, W. D. (1932). *Brit. J. Surg.*, **20**, 279.
 Palmer, W. L., and Humphreys, E. M. (1944). *Gastroenterology*, **3**, 257.
 Stewart, M. J. (1929). In Hurst and Stewart's *Gastric and Duodenal Ulcer*. Oxford Univ. Press, London.
 — (1931). *Lancet*, **2**, 565, 617, and 669.
 Wilson, L. B., and MacCarty, W. C. (1909). *Amer. J. med. Sci.*, **138**, 846.

THE USE OF ORAL CORTISONE IN PAEDIATRICS

BY

BASIL WOLMAN, M.D., M.R.C.P., D.C.H.

Assistant Lecturer, Department of Child Health, University of Manchester

Since the preliminary report describing the effects of cortisone on 14 adult patients with rheumatoid arthritis was made by Hench, Kendall, Slocumb, and Polley in April, 1949, much work recording the action of the drug in this and numerous other diseases has been reported. However, the use of a microcrystalline suspension of cortisone acetate to be administered intramuscularly either once or twice daily presented an obvious disadvantage for prolonged therapy, especially in children, so that when limited supplies of cortisone became available in tablet form the opportunity arose to test its therapeutic efficiency by mouth.

Three children with rheumatoid arthritis, one child with acute rheumatic pericarditis, and one child with nephrosis were given 25-mg. tablets of cortisone acetate ("cortone"—Merck and Co.) once, twice, or three times daily as required. The tablets are slightly bitter if dissolved in the mouth, but were easily swallowed whole by the older children. They were given crushed in milk to the two younger children. No gastric intolerance was noted.

Case 1

A 12-year-old girl was admitted to hospital on January 27, 1951, because of swelling, deformity, and restricted movement of her wrists, elbows, fingers, knees, and ankles. She had been ill since July, 1949, when vague pains occurred in several of her joints. Swelling of the knees, associated with pyrexia, was first noted in January, 1950. A diagnosis of acute rheumatic fever was made and she was admitted to another hospital. Although her fever subsided with salicylate therapy, her knees remained swollen and her ankles also became similarly affected. During the summer months her general condition improved. She was allowed to go home, but was unable to walk about very much because of the swelling of knees and ankles. In October, 1950, her wrists and fingers also became swollen and were restricted in movement. She was readmitted to hospital, where a diagnosis of rheumatoid arthritis was made and gold therapy was begun. She was reported to be worse after the second injection, and so treatment was discontinued. She was transferred to the Royal Manchester Children's Hospital for cortisone therapy.

On admission (January 27, 1951) she was a poorly nourished, chronically ill-looking child with dryness and desquamation of the skin of the arms and legs and temperature of 99° F. (37.2° C.). The heart was normal. There was no lymphadenopathy or enlargement of the spleen. There were full movements of the neck and, so far as could be ascertained, full movements of the spine. The elbows and wrists were swollen and all movements were severely limited. The shoulder-joint movements were also restricted. All fingers showed fusiform swelling. The hips and knees were fixed in flexion; the latter were grossly swollen, were incapable of extension, and had no more than 2½ in. (6.3 cm.) separation. The ankles were also swollen, with marked foot-drop and hardly any dorsiflexion. There was slight pitting oedema of the dorsum of each foot.

Her blood pressure was 105/75 and the sedimentation rate 45 mm. in one hour. The haemoglobin was 54% (Haldane), with 4,490,000 red blood cells and 10,400 leucocytes per c.mm. The eosinophils were fewer than 5 per c.mm. Radiographs showed soft-tissue swelling around the joints, no narrowing or alteration of joint spaces, and severe rarefaction of all the long bones. Electrocardiograms were normal.

On February 10 cortisone was started. She was given 300 mg. by mouth in the form of four 25-mg. tablets three times a day. This was continued for four days. She was then given 150 mg. daily for three days and 100 mg. daily for seven days, so that she received 2.35 g. by mouth in 14 days.

Within 24 hours of the beginning of treatment her temperature became normal and remained between 97 and 98° F. (36.1 and 36.7° C.) throughout the course. Within 48 hours pain in the affected joints was much less. Whereas, before treatment, passive movements had made her wince with pain, the joints, although restricted in mobility, could now be moved without hurting her. On February 13, after 72 hours' treatment, all joints except the right ankle and left elbow measured less in circumference and the range of movement had definitely increased. She seemed much brighter mentally and began to take an intelligent interest in her progress and to co-operate with the physiotherapist. On February 16, after one week's treatment, she could separate her knees by 3½ in. (8.9 cm.) and the swelling of the joints was decreasing. There was an almost complete range of movement in the wrists, although some swelling was still present. The fingers had very slight fusiform swelling and the elbows seemed normal in shape and mobility. The skin was much improved in texture. For the first time she began to knit and could comb her hair, and she could sit on the side of her bed or in a chair. At the end of the two weeks' therapy her upper limbs seemed to be perfectly normal in all respects, apart from a weakness of the hand-grip due to wasting of the small muscles of the hand. Her

knees were beginning to straighten and could be separated by 10½ in. (26.7 cm.). The ankles showed full range of movement.

During treatment, apart from the slight increase in oedema of the dorsum of both feet towards the end of the second week and an increase in blood pressure from 105/75 to 115/75, there were no serious side-effects. There was some rounding of the face and an increase in appetite by the end of the first week. Her haemoglobin rose from 54% to 80% (Haldane), her red blood cells from 3,490,000 to 4,160,000 per c.mm., and her leucocytes from 10,400 to 21,600 per c.mm. in two weeks. Her E.S.R. dropped from 45 mm. to 6 mm. in one hour after one week's treatment and to 4 mm. in one hour after two weeks. The eosinophils, fewer than 5 per c.mm. before treatment, remained at this level until the last three days of the two weeks' course, when with a lower dose of cortisone they rose to 20 per c.mm. There was no change in the fasting blood sugar, and no glycosuria.

It was decided (February 24), after two weeks' treatment, to reduce the dose of cortisone to as low a level as possible consistent with the maintenance of improvement. Accordingly 50 mg. (two tablets) daily was given for seven days, and as no deterioration in condition was noted the dose was reduced to 25 mg. (one tablet) daily.

However, after four or five days it became apparent that she was not so well. Occasional pains in the wrists and shoulders occurred, and some swellings of the right elbow and right wrist were noted. Loss of mobility was detected in these joints and also in both knees. Spikes of fever were recorded, and the E.S.R. rose to 20 mm. in one hour. On March 12, therefore, the dose of cortisone was increased to 100 mg. (two tablets twice daily), and after four days' treatment it was considered that her condition was restored. From March 16 to April 7, 50 mg. (two tablets) daily was given, and this seemed to be the amount required to suppress all disease activity.

Treatment had to be discontinued on the latter date as no further supplies of cortisone were available, and again, four days later, she began to complain of pain in the joints, peaks of fever were recorded, and decreased mobility of the joints was noted. At the time of writing (May, 1951) the knees can be abducted only 2 in. (5 cm.) from each other, her fingers show the original fusiform condition, and her other joints are slowly returning to their pre-treatment condition.

Case 2

A 3½-year-old girl was admitted to hospital on January 27, 1951, because of swelling and restricted movement of her wrists, fingers, hips, knees, and ankles. Apart from measles at the age of 7 months and tonsillitis in April, 1950, she had been a healthy child. In August, 1950, she became listless and fretful, complaining of pains in the hands, knees, and ankles, and screaming if her limbs were touched. A diagnosis of rheumatoid arthritis was made, and she was in bed for 14 weeks at home before being admitted to another hospital in November, 1950. She was transferred to the Royal Manchester Children's Hospital for cortisone therapy.

On admission (January 27) she was ill-nourished, fretful, and irritable, with marked wasting of the small muscles of the hands and legs, a retracted abdomen, and dry scaly skin. Her temperature was 98.8° F. (37.1° C.). The heart was normal, the spleen was not palpable, and no enlarged lymph nodes were present. Her wrists were swollen, the fingers were fusiform, and movements of these joints were restricted. The shoulders and elbows were normal. The left hip was fixed and internally rotated, while both knees were swollen and fixed in flexion. Both ankles were also swollen and had a limited range of movements. Any attempt to examine her or elicit passive movement was resisted. The E.S.R. was 48 mm. in one hour. The haemoglobin was 68% (Haldane), the red cells numbered 3,700,000 per c.mm., and the white cells 10,400 per c.mm., the eosinophils being fewer

than 5 per c.mm. Radiographs of the affected joints showed no diminution or alteration in the joint spaces, but there were severe rarefaction of bones and some soft-tissue swelling. The head of the left femur seemed high in the acetabulum but was not subluxated. On February 12 cortisone was started. She was given 150 mg. by mouth in the form of two 25-mg. tablets three times a day. This was continued for four days, and then she was given 100 mg. daily by mouth for eight days, so that in 12 days she received 1.4 g. of cortisone. Her temperature remained normal throughout treatment. On February 14, after 48 hours, although she was still fretful and irritable, the wrists could be passively moved without evoking screams of pain.

Two days later the movements of the wrists and fingers were much improved, but fusiform swelling of the latter was still very obvious. The knees and ankles seemed unchanged, except that she would allow examination without screaming.

On February 19, although minimal fusiform swelling of the fingers was still present, all movements of the upper limbs seemed normal. The patient was beginning to eat and seemed much brighter and happier. The left hip, however, appeared to be internally rotated more than at first, and a repeat radiograph showed subluxation of the head of the femur. On orthopaedic advice the left hip was put on traction.

The E.S.R. dropped from 45 to 12 mm. in the hour in one week and rose to 14 mm. in two weeks. In this period her haemoglobin rose from 68% to 82% (Haldane), her red blood cells from 3,700,000 to 4,500,000 per c.mm., and her leucocytes from 10,400 to 26,000 per c.mm. The eosinophils varied between 5 and 20 per c.mm. during the period of treatment. There were no side-effects apart from rounding of the face ("moon facies").

On February 24 the dose was reduced to 50 mg. daily (one tablet twice a day), and on March 3 to 25 mg. (one tablet) daily. With this amount she remained symptom-free, bright, and happy, with maximal mobility of her joints and no side-effects. On April 7 supplies of cortisone were exhausted, and treatment with it had to be discontinued. Three days after cessation of the treatment the eosinophils, which during treatment had remained below 50 per c.mm., now rose to 130 per c.mm., and have remained above 50 per c.mm. ever since. The fingers have again become fusiform, the wrists have become swollen and limited in mobility, and while the patient was being nursed on a special abduction frame the knees and ankles have almost reverted to their pre-treatment condition.

Case 3

An 8-year-old girl was admitted to this hospital on March 9, 1951, with a three-year history of pains in the hands, feet, shoulders, and neck. After a sore throat in April, 1948, she began to complain of pains in all her joints in June, and was admitted to another hospital in this city. Her temperature varied between 100 and 105° F. (37.8 and 40.6° C.), the E.S.R. between 50 and 60 mm. in one hour, and there were swelling and tenderness of the wrists, knees, and ankles. A diagnosis of acute rheumatic fever was made. For three months she was treated with salicylates, sulphonamides, and penicillin without any change in her condition, but slowly during October and November there was a gradual improvement, with subsidence of fever, return of joints to normal, and ability to walk. She was allowed to go home, and remained well till the following summer, when she had a recurrence of joint pain and swelling associated with fever, necessitating her return to bed for a period of three months. She was readmitted to hospital, where a diagnosis of rheumatoid arthritis was made, based on the swelling and deformity of her ankles, knees, and wrists, and the fusiform appearance of the fingers. By July, 1950, she had improved sufficiently to enable her to walk and to warrant her return home, continuing physiotherapy as an out-patient.

On January 30, 1951, she was readmitted to hospital with an acute exacerbation of symptoms, tachycardia, and pyrexia, all of which tended to subside during the next month. She was transferred to the Royal Manchester Children's Hospital on March 9, 1951, for cortisone therapy.

On admission she was a pale undernourished child with palpable glands in the groin, axillae, and neck. The heart was not enlarged and sounds were normal. Blood pressure was 95/65, and the tip of the spleen could just be felt. Her temperature and pulse rate were raised on admission, but settled to normal levels during the subsequent week.

Neck movements, backwards and forwards and from side to side, were restricted. Wrists, elbows, knees, and ankles were swollen and severely limited in movement. All fingers showed typical fusiform swelling. Appetite was poor.

Blood investigations showed: haemoglobin, 60% (Haldane); 3,280,000 red blood cells per c.mm.; 18,400 white blood cells and 40 eosinophils per c.mm.; E.S.R. 84 mm. in one hour.

Cortisone therapy was started on March 17. Three 25-mg. tablets were given orally morning and night and two at midday, making 200 mg. a day, for three days. Within 48 hours the girl was brighter, and was talking to other children and the staff. Although there was no increase in range of movement, pain on passive movement of all joints had disappeared.

After three days' treatment the eosinophil count had dropped to 1 to 2 per c.mm. and some increase in range of movement of all the joints was noted. She was then given 150 mg. (two tablets thrice daily) orally for three days, and 100 mg. (two tablets twice daily) for 11 days. During this period there was a steady increase in range of mobility of all affected joints and a gradual diminution in swelling. On March 23, after a week's treatment, the E.S.R. dropped to 12 mm. in one hour, and on April 4, after 17 days' treatment, she began to take a few halting steps. On this day the dose of cortisone was reduced to 50 mg. daily (one tablet twice a day) in the hope that dosage could be maintained at this level, but four days later supplies of cortisone became exhausted and treatment had to be abandoned. She therefore received 2.4 g. of cortisone over a 22-day period.

The improvement in general behaviour and mentality was striking, being noted within 48 hours of the introduction of treatment. The temperature remained normal throughout and her blood pressure did not vary. Her weight increased from 32 lb. 2 oz. to 34 lb. 12 oz. (14.6 to 15.8 kg.) by the sixth day of treatment and to 35 lb. 12 oz. (16.2 kg.) by the end of treatment, but there was no oedema and the gain in weight was attributed to marked improvement in appetite. No side-effects were noted. The eosinophils remained low until the dose of cortisone was reduced to 100 mg. daily, when there was a slight rise in the eosinophil count and a further rise when the dose was dropped to 50 mg. daily, but there was no great increase and no evidence of the "rebound" phenomenon after cessation of treatment.

Four days after treatment was stopped it was noted that the child was not as bright or as happy as formerly, and she refused to make any attempt to walk because of pain in her knees and ankles, whereas formerly she had been eager to do so. A week after treatment was discontinued she began to show evening elevations of temperature, which have persisted ever since, and at the time of writing, one month later, joint movement is almost back to its pre-treatment range and swelling is almost as severe as formerly. The E.S.R. has risen to 93 mm. in one hour.

Case 4

An 11-year-old boy was admitted to hospital on February 11, 1951, having been listless and off colour since an attack of influenza in mid-December and tonsillitis in January, for which he had received penicillin therapy. One week before admission he had complained of pains in the shoulders and

abdomen, but swelling of the joints had not occurred. He was reported to have had an attack of rheumatic fever in 1948 necessitating rest in bed for five weeks at home.

On admission his temperature was 99.5° F. (37.5° C.) and pulse rate 100. There were no nodules or erythematous rashes. The heart was not enlarged, but a systolic murmur (grade 3) was noted at the apex. Examination of the blood showed 82% haemoglobin (Haldane), 4,000,000 red blood cells, 12,600 white blood cells, and E.S.R. 102 mm. in one hour.

His condition remained unchanged until February 18, when in the evening he complained of pains in the left side of the chest. His temperature rose to 101° F. (38.3° C.) and his pulse rate to 120. A friction rub was audible all over the praecordium. During the next few days his temperature remained above 100° F. (37.8° C.) and his pulse rate above 120, and by February 24 his condition had deteriorated. He was orthopnoeic and slightly cyanosed. His heart was grossly enlarged, the borders of cardiac dullness to percussion extending into the axillae on both sides, beyond the maximal impulse that could be felt in the fifth left intercostal space 7 cm. from the mid-sternum. A systolic thrill and a to-and-fro friction rub were noted over the central precordial area, and a harsh systolic murmur was audible at the apex. Pulsus paradoxus was observed, and the blood pressure was 110/55. Both lung bases were dull to percussion, and an area of bronchial breathing and increased voice conduction could be made out at the left base. The neck veins were engorged to a point half-way between clavicle and jaw, while the liver edge was easily palpable. There was no oedema or ascites. The E.S.R. was 99 mm. in one hour, white cell count 21,200, and eosinophils 5 per c.mm. Blood culture was sterile. An x-ray film of the chest showed gross cardiac enlargement with evidence of pericardial effusion.

A low-salt diet was ordered and cortisone therapy was started. Three 25-mg. tablets were given morning and night and two tablets at midday, so that he received 200 mg. daily for two days.

On the second day of treatment the temperature reached only 99° F. (37.2° C.) and he seemed a little more comfortable. After two days' treatment there was a distinct improvement. The temperature was normal; tachycardia, however, was still present, but there was no dyspnoea or cyanosis. The maximal cardiac impulse was not as tumultuous or diffuse, and could be located 5 cm. to the left of the sternum in the fifth space. Pericardial friction had disappeared; a systolic murmur only was audible at the apex. Jugular venous pressure was normal. The liver was no longer palpable and no oedema had occurred.

X-ray films confirmed the diminution in cardiac size. It was felt that, as some improvement in cardiac function had occurred, the danger of a cortisone-induced salt retention precipitating cardiac failure was less likely, and the dose was increased to four tablets three times a day (300 mg. daily), which was given for four days.

On March 2, after six days' treatment, rounding of the face was noted. The E.S.R. was 45 mm. in one hour. Temperatures had been normal since the second day of treatment, but the pulse rate was still 110. The size of the heart appeared to be unchanged. Jugular venous pressure seemed to be slightly raised again and the liver edge was palpable. Moist sounds were noted throughout both lungs. Mersalyl, 0.5 ml., was given intramuscularly, and after a good diuresis on the two subsequent days signs of congestion disappeared. Cortisone was reduced to 150 mg. daily (two tablets three times a day) for four days and then to 50 mg. daily (one tablet twice a day) for four days. The patient therefore received a total of 2.4 g. in 14 days. The eosinophil count, which had remained low during the first 10 days' treatment, began to rise during the last four days, when low doses (50 mg. daily) were given.

On March 6, before the cortisone dose was reduced and despite continued clinical improvement, there was a

secondary rise in E.S.R., recorded as 58 mm. in one hour on that date and 106 mm. 10 days later.

During the week after cessation of treatment he had irregular peaks of temperature, a further rise in pulse rate, and an increased respiratory rate, and complained of occasional joint pains. These manifestations gradually subsided, and up to the time of writing he has been asymptomatic and afebrile. The pulse rate has dropped to 90 and the E.S.R. has fallen to 70 mm. in one hour. The maximal cardiac impulse is now 6 cm. from the mid-sternum just outside the mid-clavicular line, and systolic and diastolic murmurs have become recognizable at the apex.

Case 5

A 2½-year-old boy was admitted to hospital on February 14, 1950, with a four to five months' history of recurring bouts of puffiness of the face and legs. Apart from frequent colds, and sore throats for a short period 18 months previously, his general health and development had been satisfactory.

On admission he showed oedema of the eyelids, face, hands, and feet. There was some ascites. The heart and lungs were normal. Blood pressure was 125/85. The urine contained 3 g. of albumin and scanty red blood cells. His weight was 35 lb. (15.9 kg.). The blood contained 86% haemoglobin (Haldane) and 13,400 white cells per c.mm. Blood urea was 25 mg. per 100 ml., serum cholesterol 400 mg. per 100 ml., total serum protein 5.49 g.%, serum albumin 1.8 g.%, and serum globulin 3.69 g.%, the A/G ratio being 0.49.

During the next month his oedema fluctuated in severity, but on April 2, following an attack of bronchopneumonia with high fever seven days previously, a diuresis began and he lost 8 lb. (3.6 kg.) in weight. He was discharged from hospital on April 13, with slight oedema of his legs only, and 1 g. of albumin in his urine. His serum cholesterol was 680 mg. per 100 ml., and his total serum proteins were 3.71 g.%, with an A/G ratio of 0.3.

He remained well for one month at home and was then readmitted to hospital on May 16 with recurrence of oedema and ascites. The urine showed 5 g. of albumin and scanty red cells. Throughout May, June, and July he experienced numerous exacerbations and remissions but no true diuresis. His serum cholesterol reached 920 mg. per 100 ml. on September 23, and between that date and the end of the year he was transfused on several occasions with concentrated plasma without any effect. He had a moderate diuresis one week after an attack of mumps in January, 1951, but by mid-February his oedema and ascites were as marked as previously. His weight was 38 lb. 3 oz. (17.3 kg.). Blood pressure was 115/75.

On February 15 cortisone was started. Four 25-mg. tablets were given three times daily for three days, followed by two tablets twice daily for five days, and then one tablet was given morning and night on the last day of a nine-day course, so that he received 1,450 mg. in all.

His weight remained unchanged throughout treatment and his oedema and ascites did not vary. His blood pressure increased from 115/75 to 130/90. His eosinophils, 250 per c.mm. before treatment, dropped to fewer than 5 per c.mm. 24 hours later, remaining low throughout the period of treatment and increasing thereafter. Three days after cessation of treatment diuresis began and he lost over 7 lb. (3.2 kg.) in weight. The urinary albumin decreased to 1 g. and the blood pressure returned to 110/70. During the next six days he lost all his oedema, and when discharged from hospital on March 7 he weighed 28 lb. (12.7 kg.), showed a little ascites only, and had less than 1 g. of albumin in his urine.

When seen in the out-patient clinic on April 19 he was free of oedema and ascites. His urine contained 0.5 g. of albumin, and a blood examination showed a serum cholesterol of 170 mg. per 100 ml., and serum proteins of 5.72 g.%, with an A/G ratio of 1.5.

Discussion

Since Hench's original report two years ago, the striking benefit produced by injections of cortisone (17-hydroxy-11-dehydrocorticosterone; compound E) in various diseases has been fully confirmed. Thorn and his co-workers (Thorn *et al.*, 1950) have reviewed the clinical usefulness of the hormone. Suppression of the manifestations of rheumatoid arthritis has been confirmed both in America (Boland and Headley, 1949) and in this country (Copeman *et al.*, 1950). Juvenile rheumatoid arthritis has responded to this treatment in the same way as the adult form (Freyberg, 1950; Rosenberg, personal communication, 1950). The use of an oral form of cortisone, however, is much to be preferred in the treatment of children, and in the first three cases here reported the same striking beneficial results were demonstrated with the use of the hormone in tablet form. Moreover, improvement occurred as quickly after oral therapy as when parenteral therapy was used. After only 48 hours' treatment, passive movements of the affected joints could be carried out with less pain, indicating a reduction in stiffness of the muscles and joints and lessening of tenderness and pain on motion. After 72 hours' treatment there was increased mobility and some diminution in swelling.

The initial dose of cortisone was 300 mg. daily in Case 1, 200 mg. daily in Case 3, and 150 mg. daily in Case 2, and a substantial reduction in dose was made after the first three to four days. Cortisone administered by mouth was highly effective in suppressing disease activity without serious side-effects, and control could be maintained by giving 50 mg. daily to Case 1 and 25 mg. daily to Case 2, which meant in effect giving one or two tablets a day—a simple enough procedure to keep so serious a disease in abeyance. Relapse occurred, however, when therapy was reduced below this point and when it had to be discontinued entirely. The sedimentation rate, haemoglobin, red cells, and white cells reacted in the same way with this type of therapy as has been reported with the use of intramuscular injections of cortisone (Hills *et al.*, 1948; Thorn, 1949). In all three children the E.S.R. became normal after one week's treatment, but began to rise again after treatment was discontinued. There were substantial increases in haemoglobin and red blood cells in all three patients.

The child (Case 4) with acute pericarditis showed a dramatic initial response 48 hours after treatment with 200 mg. daily of cortisone was begun. Pericardial friction disappeared, temperature returned to normal, dyspnoea and cyanosis were relieved, and there was some diminution in cardiac size. His condition appeared to be stationary during the remainder of the 14-day period of treatment. During the week after treatment, however, there were signs of increased activity as shown by occasional pains in the joints, spikes of fever, and an increasing pulse rate. During the two months that have elapsed since then there has been a slow and gradual decrease in cardiac size, although systolic and diastolic murmurs persist. The pulse rate has returned to normal, the temperature has remained within normal limits, and the course of the disease has undoubtedly been shortened.

The E.S.R. showed a characteristic response. After a preliminary fall from 99 to 49 mm. in the hour there was, despite continued clinical improvement, a secondary

rise to 106 mm. 14 days later. Since then there has been a slow and steady decrease to normal levels. The result achieved in this case, using 200 mg. of cortisone daily for the first two days—a dose similar to that described by Hench using parenteral therapy—was comparable to that described by Barnes (1950), and by Massell *et al.* (1950), using intramuscular injections. By virtue of its salt- and water-retaining properties, and in the presence of impaired cardiac function, cortisone is capable of producing congestive failure, but, by the use of a low-salt diet and a mercurial diuretic at the first sign of congestion, serious side-effects were prevented.

The child (Case 5) with nephrosis gave a 16-months history of exacerbations and remissions of his oedema and ascites, showing characteristic diuresis after episodes of high fever associated with pneumonia and mumps. On no occasion, however, had diuresis been complete nor had albuminuria entirely disappeared. Chemical examination of the blood showed abnormalities. Three days after a nine-day period of administration of oral cortisone a diuresis began during the course of which he lost all his oedema and ascites. Albuminuria virtually disappeared and blood tests returned to normal. At the time of writing he had remained well for nearly three months, the longest remission he has ever experienced.

A similar diuretic response has been obtained in this disease by Keith *et al.* (1950) and Barnett and his co-workers (1950) using parenteral cortisone, but the advantage of being able to give the hormone by mouth instead of by injection to an oedematous child need hardly be stressed.

Cortisone given by mouth, therefore, was capable of producing the same type of response as when given by injection in patients suffering from rheumatoid arthritis, rheumatic fever, and nephrosis. Absorption from the gastro-intestinal tract appeared to be certain and reliable provided the total daily dose was divided and given in two or three portions. Its actions came into effect as quickly as when parenteral administration was used. No gastric intolerance was noted and side-effects were minimal, but these were no different from those noted with the other type of cortisone administration, and were perhaps less marked. Slight elevation of the blood pressure was noted in one patient with rheumatoid arthritis and in the patient with nephrosis during the period of treatment, but there was an immediate return to normal after treatment had ceased. The danger of producing salt- and water-retention and precipitating cardiac failure in patients with impaired cardiac function is always present, but this danger is probably more easily avoided when the dose of cortisone can be administered in divided amounts by mouth. Rounding of the face, increase in appetite, and a brightening of mental outlook were noted in all patients during the first week's treatment—an effect similar to that noted when the drug was given by injection.

Freyberg *et al.* (1950) used 100-mg. tablets in the treatment of four adult patients with rheumatoid arthritis, and considered that in all respects the clinical effects of orally administered cortisone were comparable to those of the hormone given parenterally. Kuzell and Schaffarzick (1950) treated 11 patients with various types of arthritis with the 25-mg. tablets and claimed to obtain the best results by giving two-thirds of the daily dose on rising and one-third on retiring. They felt that 1.25 to 3 mg. of cortisone given orally was required to

equal the effect of 1 mg. given by injection. Boland and Headley, in a study designed to compare the effectiveness of the oral and intramuscular routes of administration of the drug, were able to suppress disease activity and maintain control in 22 out of 23 adults with rheumatoid arthritis, using the oral method, but they found that larger maintenance doses were needed when the drug was given by mouth.

Summary

Cortisone given in tablet form by mouth was capable of suppressing disease activity in three children with rheumatoid arthritis and one child with rheumatic pericarditis.

Control of the former disease was obtained by the administration of one to two tablets a day.

Diuresis was produced and remission obtained in one patient with nephrosis after a course of treatment with cortisone.

Oral cortisone was as quickly and as completely effective in the treatment of these diseases as parenteral cortisone, the same amount of the drug being found to be necessary, so long as the total daily dose was given in divided amounts two or three times a day.

The ease of administering a tablet preparation of cortisone, particularly for prolonged therapy in children, is stressed.

My thanks are due to Dr. Augustus Gibson, medical director, Merck and Co., New Jersey, U.S.A., who kindly supplied the tablets of cortisone acetate; to the physicians who referred the above patients; and to Professor Wilfrid Gaisford for permission to treat them and for valuable advice in the preparation of this report.

REFERENCES

- Barnes, A. R. (1950). *Proc. Mayo Clin.*, **25**, 478.
 Barnett, H. L., McNamara, H., McCrory, W., Forman, C., Rapoport, M., Michie, A., and Barbero, G. (1950). *Amer. J. Dis. Child.*, **80**, 519.
 Boland, E. W., and Headley, N. E. (1949). *J. Amer. med. Ass.*, **141**, 301.
 — (1951). *Ibid.*, **145**, 8.
 Copeman, W. S. C., Savage, O., Bishop, P. M. F., Dodds, E. C., Gottlieb, B., Glyn, J. H. H., Henly, A. A., and Kellie, A. E. (1950). *British Medical Journal*, **2**, 849.
 Freyberg, R. H. (1950). *Bull. N.Y. Acad. Med.*, **26**, 206.
 — Traeger, C. T., Adams, C. H., Kuscu, T., Wainerdi, H., and Bonomo, I. (1950). *Science*, **112**, 429.
 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.
 Hills, A. G., Forsham, P. H., and Finch, C. A. (1948). *Blood*, **3**, 755.
 Keith, N. M., Power, M. H., and Daugherty, G. W. (1950). *Proc. Mayo Clin.*, **25**, 491.
 Kuzell, W. C., and Schaffarzick, R. W. (1950). *Stanford med. Bull.*, **8**, 212.
 Massell, B. F., Warren, J. E., Sturgis, G. P., Hall, B., and Craig, E. (1950). *New Engl. J. Med.*, **242**, 641, 692.
 Thorn, G. W. (1949). *Trans. Ass. Amer. Phys.*, **62**, 233.
 — Forsham, P. H., Frawley, T. F., Hill, S. R., Roche, M., Staehelin, D., and Wilson, D. L. (1950). *New Engl. J. Med.*, **242**, 783.

In his annual report for 1950 the medical officer of health of Birmingham discusses social conditions in that city. Slum clearance is a pressing problem, for there are still 28,917 back-to-back houses. "Houses forming a continuous row abutting on to the street are separated at the rear by a 4½-in. wall from similar houses, and facing these across the courtyards are other little houses of similar type, all massed together and using w.c.s and washhouses in common." A survey carried out in 1946 showed that in the central ward of the city there were 36,000 houses, 18,265 of them being of the back-to-back type, 4,337 being without internal water, and 21,225 being without a separate w.c. The school medical officer of Liverpool, in his annual report for 1950, states that 24,849 children were found during the year to show some evidence of verminous infestation or were very dirty. Of the children examined by school nurses during cleanliness surveys 20.9% were found at least once during the year to be infested.