of events? Why does the cardiac patient pass into a dying state with a resting minute volume of circulation the same as that of an upright soldier?

The realization of ignorance brings its gleam of hope that continued research will add to our therapeutic power: cardiac surgery and new technical developments in investigation are adding daily to our knowledge and extending our experience in depth. In time some of the pictures crudely sketched in these lectures will be more clearly perceived, and be submitted once again to a much more rational and complete interpretation than we can give to-day.

(Figs. 5, 6, and 7 are reproduced from *Acta Medica Scandinavica*, 1952, Supplement 266, p. 701, by kind permission of the Editor.)

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Whales are popular among doctors nowadays. Not only are their pituitary glands a useful source of A.C.T.H., the whales are also the quarry of the cardiologist. Dr. Paul D. White has recently returned to Boston from Alaska with a one-ton beluga whale's E.C.G. The electrodes were brass-headed harpoons (*Time*, August 25).

RHEUMATIC FEVER

SOME OBSERVATIONS ON A.C.T.H., CORTISONE, AND SALICYLATE THERAPY

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Hench and his colleagues (1950) have demonstrated the rapid benefit afforded by A.C.T.H. and cortisone to sufferers from rheumatic fever. They could not, however, determine whether such treatment lessened the incidence or degree of valvular damage. They also showed that these hormones have a profound effect on the metabolism of protein, fat, carbohydrate, and electrolytes, and that the continued administration of them led to some of the clinical and biochemical changes observed in Cushing's syndrome. Treatment with salicylate has hitherto been the basic method and evidence is accumulating that this well-tried remedy actually engenders adrenocortical excess. In this paper we give an account of the use of A.C.T.H. and cortisone in four selected cases of rheumatic fever and describe the response of four other cases to treatment with salicylates. We add to the evidence that salicylate has an A.C.T.H.-like effect, and we give our present impressions of the value of A.C.T.H., cortisone, and salicylate in the treatment of rheumatic fever.

Cortisone Treatment

We gave the cortisone to severely ill patients who had not responded to salicylates. The dosage in each case is set out in Fig. 1. Cortisone acetate was given by intramuscular injection daily for six days each week. We thought at first that the hormone could be discontinued once we had abolished the tachycardia, corrected the anaemia, and reduced the raised E.S.R. to normal. As will be seen, recrudescence of the disease often followed the cessation of treatment at such a stage. Because of this and the similar experience of others (Dorfman *et al.*, 1951) we increased the period of therapy by at least four to six weeks, with the aim of suppressing these signs. The duration of treatment varied from 44 to 110 days.

FIG. 1.—Effects of cortisone on patients who did not respond to salicylates.

Case 1

The patient, a boy aged 9, had no previous history of rheumatic disease. Two weeks before admission he developed a sore throat and then arthritis. When admitted on October 12, 1950, he was pyrexial, with a tachycardia, and a systolic murmur was heard at the mitral area. With salicylate therapy the pulse rate and temperature fell to normal by the fifth day, and by November 29 the E.S.R. was 16 mm. (Westergren). He was discharged on December 20, only to be readmitted five days later with a relapse. Pyrexia and tachycardia persisted despite penicillin and salicylate therapy. Because of tinnitus the dose of salicylate was reduced, and three days later he was worse and there were signs of pericarditis. On January 23, 1951, a typical erythema marginatum appeared. The lower lobe of the left lung was compressed, the liver was enlarged, and the feet and scrotum were oedematous. Haemoglobin was 66% and the E.S.R. 58 mm.

Cortisone treatment was begun on January 24. The next day the rash was fading and no friction rub was heard. He was afebrile one week later, when the displacement of the apex beat was less and tachycardia had decreased. During the second week, with mercurial diuretics, the liver was less enlarged and the oedema cleared. After four weeks' treatment the dose was reduced to 50 mg. daily. A short bout of fever followed at once. During the following weeks it was evident that the disease was not controlled. When cortisone was discontinued in the ninth week, high fever, tachycardia, and joint pains returned. They were soon relieved by 75 mg. of cortisone daily. Reduction of dosage in the fourteenth week was followed by transient fever. When treatment was discontinued after four months moderate fever returned. He was given aspirin, and after his transfer to Queen Mary's Hospital, Carshalton, the fever subsided and he felt well. On discharge from that hospital there were no signs of carditis.

Case 2

A boy aged 15 was admitted on March 5, 1951. He was known to have heart disease due to rheumatic fever and chorea. Four days before admission he developed joint pains, sweating, and fever. On admission he had a sore throat and the left wrist and right knee were inflamed. His heart rate was 110, and blood pressure 160/20. The heart was enlarged to the mid-axillary line, and signs of mitral stenosis and aortic incompetence were present. Haemoglobin was 73%, and the E.S.R. 54 mm. He was given acetylsalicylic acid, 8 g. daily. By the seventh day he was afebrile and his pulse rate was 80. On March 15 he developed fever due to an alveolar abscess; penicillin was given and the tooth extracted. Blood cultures were negative. Pyrexia continued, and a few days later he had pains in his knees and ankles. Pericardial effusion was suspected. Haemoglobin was 67%, and the E.S.R. 60 mm.

On April 13 penicillin and salicylates were discontinued and cortisone therapy was begun. Two days later his general condition was worse. He was drowsy, his joints were still painful, and his temperature did not subside until April 19. Blood cultures taken meantime were negative. By April 23 he was much improved. When the cortisone dosage was reduced to 75 mg. daily, rheumatic nodules appeared; pyrexia, tachycardia, and joint pains persisted for five days after the dosage was restored. In the seventh week another attempt at reduction of dosage was followed by a rise of temperature. Cortisone was finally discontinued after 14 weeks, and was withheld even though he became pyrexial and the E.S.R. had increased. We hoped that this was a manifestation of temporary adrenocortical insufficiency (see below). His nodules had slowly decreased in size and were not visible by this time. A few days later the fever settled, although the E.S.R. did not become normal for three weeks. There were no symptoms during this period. He subsequently remained well, and he thought that his dyspnoea was no worse as a result of this attack of rheumatic fever.

Case 3

A boy aged 9, with established rheumatic heart disease following rheumatic fever and chorea, was admitted on January 25, 1951, with severe epistaxis; signs of mitral stenosis and aortic incompetence were also present. Epistaxis recurred, and the haemoglobin fell to 46%. He was transfused on February 3 and immediately became febrile. On February 6 he had joint pains, dyspnoea, and tachycardia. There were scattered petechiae, and a pericardial friction rub was audible. Blood cultures were negative. On February 7 calcium aspirin was administered. On the following day the patient had no pain, he was pyrexial, and the rub was no longer audible. On February 16 the temperature rose again, he was dyspnoeic, and the heart was further enlarged. On February 21 a pericardial rub was again audible, the haemoglobin had fallen to 54% and the E.S.R. was 55 mm.; treatment with cortisone was begun. Two days later he was brighter and less dyspnoeic. The friction rub was not audible after February 26. Oedema then developed, but he was still on a high dosage of aspirin. This was discontinued, mercurials were given, and the oedema subsided. Transient pyrexia followed reduction of cortisone dosage. He maintained his recovery when cortisone was discontinued after 44 days.

Case 4

A girl aged 14, with no previous history of rheumatism, was admitted to another hospital on April 21, 1951. Three weeks before admission she had a sore throat followed by arthritis and fever. On admission her heart was enlarged to the anterior axillary line, and a systolic murmur was audible at the mitral area. Haemoglobin was 70% and the E.S.R. 126 mm. (Westergren). Joint pains subsided on 150 gr. (10 g.) of sodium salicylate daily, but fever persisted. On April 28 the serum salicylate was only 15 mg. per 100 ml. and dosage was increased to 180 gr. (12 g.) daily. On May 4 the serum level was 38 mg. per 100 ml. and the dosage was halved for a few days. On May 7 widespread nodules appeared and the temperature rose; a week later a pericardial rub was heard.

On May 21 she was transferred to this hospital. Her general condition was worse. Nodules lay as rows of beads over the extensor tendons of the fingers and toes, over the wrists and ankles, on the ulnar borders of the forearms, over the elbows and knees, scapulae, and occiput. Cortisone treatment was begun immediately. Two days later she was much improved. The friction rub was not heard after four days, she was afebrile, and the heart was smaller. The rheumatic nodules rapidly decreased in size, and after two weeks' treatment could not definitely be discerned, except over the left elbow, where they persisted until July 18. The haemoglobin and E.S.R. had become normal one month before, at which time the systolic murmur was not audible. She had cortisone for 58 days and

FIG. 2.—Showing response to A.C.T.H. in Case 4.

was transferred to a convalescent home. She later relapsed there, and was readmitted to this hospital and given A.C.T.H. (see below).

A.C.T.H. Treatment

Case 4 was transferred to a convalescent home on July 29, 1951, 12 days after cortisone was discontinued. She there gained weight rapidly. During August haemolytic streptococci were cultured from the throat and she was given penicillin on September 6. Her temperature rose and a loud systolic murmur was heard. The E.S.R. was 100 mm. On September 8 she was brought back to this hospital and treatment was promptly begun. A.C.T.H., 10 mg., was given by intravenous drip overnight, and then 20 mg. every six hours intramuscularly. After two days she was afebrile and the heart rate was normal (Fig. 2). The systolic murmur remained rough and she had occasional joint pains. After 20 days the A.C.T.H. was increased to 15 mg. every four hours. From then on there was progressive improvement and the murmur softened. After 28 days A.C.T.H. was discontinued. She was gradually got up and remained well. A soft systolic murmur has persisted. There is no sign of cardiac enlargement on radioscropy.

Salicylate Treatment

With the hormone-treated cases above we found that the serum total cholesterol rose to a high level. We therefore decided to find if a similar increase occurred with salicylate treatment. We selected patients with first attacks of rheumatic fever. Fig. 3 gives the results of laboratory investiga-

FIG. 3.—Showing results of treatment with salicylates.

tions and the dosage of acetylsalicylic acid. The drug was given as "berex" tablets. Each tablet contains acetylsalicylic acid, 3.7 gr. (250 mg.), and calcium succinate, 2.8 gr. (190 mg.). Dosage was designed to keep the level of salicylate in the serum above 30 mg. per 100 ml. (as salicylic acid by the Tarnoky method (Tarnoky *et al.*, 1950)). This high dosage was well tolerated.

Case Summaries

Case 5.—A girl aged 8 was admitted on October 9, 1951, and discharged on November 22. She had tonsillitis eight days before admission, and four days later her legs became painful. On admission there was erythema over both knees, which were inflamed. She was pyrexial, her heart rate was 120, and the heart sounds were soft. During the first four

days her temperature and pulse rate were raised, but the joint inflammation subsided. She was then treated with berex tablets. The temperature became normal overnight, while the pulse rate returned to normal after seven days. No cardiac murmurs were heard at any time. Her anti-streptolysin (A.S.O.) titre reached 3,000 units on November 1.

Case 6.—A girl aged 5 was admitted on September 21, 1951, and discharged on November 13. Five days before admission she developed pain in her knees. When she was admitted these joints were warm and tender, her temperature was 102.8° F. (39.3° C.), and the pulse rate was 134. A soft systolic murmur was audible at the apex. Treatment was begun the next day. She quickly improved, and the pulse rate was normal by the end of the first week. The soft systolic murmur was not heard after the third week. The A.S.O. titre reached 840 units on October 3.

Case 7.—A girl aged 17 was admitted on November 7, 1951, and discharged on January 24, 1952. Before admission she had a sore throat, followed a week later by pain in the lower limbs. She was admitted the next day with a temperature of 103° F. (39.4° C.). There was widespread joint inflammation, with erythema over the ankles; the heart sounds were softened. Treatment was started the same day. After four days the joints were normal. On the fifth day she was afebrile. During the second week a soft systolic murmur was audible at the apex, but this diminished and was not audible on discharge. Cardioscopy then showed the heart to be normal in size. The A.S.O. titre was 400 units on November 12.

Case 8.—A girl aged 14 was admitted on November 12, 1951, and discharged on March 13, 1952. Early in October she had a sore throat, followed a week later by pain in the right knee. This responded to salicylates at home, but when the dose was reduced the knee again became painful and pyrexia recurred. On admission the temperature was 101° F. (38.3° C.), and pulse rate 130. The right knee and ankle were inflamed; the heart appeared normal. Treatment was begun the next day. After two days she was afebrile, and after four days there was no tachycardia. Pain in the left elbow recurred on November 21, but subsided when the dosage was increased. After reduction of the dosage on November 29 the temperature rose and joint pain recurred. Dosage was again increased and she became well. The A.S.O. was 400 units on November 26.

Laboratory Investigations

During treatment weekly estimations of haemoglobin (alkaline haematin method), white blood count, E.S.R. uncorrected (Wintrobe), and serum sodium, potassium, chloride, and total cholesterol were made. Consistent changes were observed only in the haemoglobin, E.S.R., and serum total cholesterol. These results are shown in Figs. 1 and 2. The haemoglobin rose steadily until discharge, when the levels were all above 80%. In all cases E.S.R. readings fell with the initial therapy, only to rise again on reduction or termination of treatment. At discharge all readings were normal or nearly so. The serum cholesterol showed a steady rise during the first month with cortisone, A.C.T.H., and salicylate treatment. With cortisone, reduction of dosage was promptly followed by a fall in the serum cholesterol. In two of the salicylate-treated cases (Cases 5 and 7) cholesterol estimations were done daily for the first few days, and an initial fall of serum cholesterol was observed in both. These investigations were made because A.C.T.H. is reported to differ in its action from cortisone in that there is a fall of the serum cholesterol during the first days of administration (Conn *et al.*, 1950).

Side-effects

Cortisone Treatment.—Special care was taken to look for any of the side-effects that have been reported to follow hormone therapy (Hench *et al.*, 1950). No patient showed any mental disturbance during treatment. The initial torpor

was soon replaced by normal mental vigour. The appetite was increased—enormously in Case 2. Purple striae developed on the back in Case 2 and on the buttocks in Case 4. Slight acne was seen in Cases 1 and 2. Rounding of the face appeared in all cases by the end of the first month. It became very marked in Case 2, in which neck and trunk thickened with obesity. Case 1 also showed deposition of fat on the trunk after two months. Oedema was present in Case 1 at the start of treatment. Case 3 developed oedema after five days' treatment; by an oversight he was still taking a large dose of aspirin. Mercurial diuretics soon cleared the oedema.

A.C.T.H. Treatment.—Case 4, who had gained weight while away at the convalescent home, developed a rounded face and a dorsal pad of fat during A.C.T.H. treatment. Thin red radiating striae developed on both breasts, similar to those observed during pregnancy. The patient, although 14 years old, had not yet menstruated.

Salicylate Treatment.—All patients showed rounding of the face and an increased appetite. Case 7 developed red radiating striae on both breasts similar to those observed in Case 4.

Discussion

Response to Hormone Therapy.—The presence or absence of a past history of rheumatic disease seems to have had no bearing on the response to treatment. Within a few days the patients became symptom-free and afebrile. Signs of cardiac inflammation disappeared; the pulse rate fell to normal, the heart size diminished, and in the two cases with a first attack the systolic murmur disappeared. If we accept the old teaching that nodules are evidence of active endocarditis, then their rapid dissolution in Case 4 may have been parallel to a resolution of the endocarditis. After reduction of dosage or termination of treatment there usually was a return of fever, and often of joint pain; one patient (Case 2) even developed nodules. Sprague *et al.* (1950) attribute this flare-up to adrenocortical insufficiency induced in the patient by the exogenous cortisone. When cortisone is administered to experimental animals the adrenal cortex decreases in size, and after the cortisone is discontinued several days must pass before the cortex is restored (Winter *et al.*, 1950). Once the adrenal cortex is restored the flare subsides if the rheumatic activity that is present is slight enough to be suppressed by endogenous adrenal activity. Wilson and Helper (1951) have seen similar flares following A.C.T.H. treatment, and thought them to be due to an inhibition of the anterior pituitary. Case 1 showed a true and continued relapse when cortisone was discontinued. Here the disease may not have reached its natural termination, or a throat infection present at that time may have been responsible.

A.C.T.H. was given to only one patient—Case 4 of the cortisone series, when she had a recurrence due to a throat infection. Improvement followed at once, but the dosage was increased from 20 mg. every six hours to 15 mg. every four hours before satisfactory control was obtained. We did feel that the A.C.T.H. had averted a serious recurrence, but the persistence of a systolic murmur seemed to indicate that valvular damage had occurred.

Side-effects.—We saw very few of the side-effects found by other workers, and none was of serious consequence. The striae do persist after their colour has faded. We could not weigh our patients while they were confined to bed, but weight gain was apparent in all and continued after the treatment ceased. All our patients were young and growing, and some gain in weight was to be expected, but the obesity of two of them lingered.

Adverse Effects.—The most serious early adverse effect that has been reported is an increase of heart failure in the days following the beginning of treatment (Carlisle, 1950; McEwen *et al.*, 1950). This increase is due to the retention of sodium and water, and usually abates when a diuresis occurs on continued treatment or a mercurial diuretic is given. The low-salt diet may have protected

our patients. Cortisone and A.C.T.H. mask the presence of infection, and it is likely that a throat infection might go unnoticed by the patient. This is an added reason for precautions against cross-infection in the ward. The prophylactic administration of penicillin is recommended by some. A throat swab should certainly be taken every week.

Corticogenic Hypothyroidism.—Fig. 1 demonstrates the rise of the serum cholesterol that occurred in our cases treated with cortisone, and Fig. 2 the rise with A.C.T.H. therapy. This response to these hormones has been noted by Adlersberg *et al.* (1950) and by Conn *et al.* (1950). Wolfson *et al.* (1951) believe that this rise is due to the development of hypothyroidism. They have demonstrated that A.C.T.H. and cortisone lower the plasma-bound iodine level and decrease the radioactive iodine uptake of the thyroid, and they call this "corticogenic hypothyroidism."*

Effect of Salicylates

We sought for and found changes in the serum cholesterol level when cases of rheumatic fever were treated with salicylates (Fig. 3). The response of serum cholesterol to A.C.T.H. differs from that of cortisone in that there is a fall during the first days of administration (Conn *et al.*, 1950).

In two of the salicylate-treated cases daily readings were begun, and these showed an initial fall of serum cholesterol—that is, resembling the response to A.C.T.H. This finding is in line with the view of Hetzel and Hine (1951), based on other evidence, that salicylate leads to an increase of A.C.T.H. production. We admit that salicylate may have an antithyroid effect by combining directly with available iodine, but we have been unable to do this *in vitro* as Bull and Fraser (1950) were able to do for resorcinol, and the initial fall of serum cholesterol favours the first explanation.

A more elaborate investigation is clearly necessary to determine whether the rise of serum cholesterol with salicylate therapy is due to hypothyroidism and whether it is mediated via the pituitary-adrenal axis. Salicylate and cortisone both have an antipyretic effect and reduce the E.S.R. They both cause retention of sodium chloride and water, and then diuresis (Reid *et al.*, 1950). They both increase uric acid excretion and cause loss of potassium and nitrogen. There is decreased glucose tolerance (Cochran *et al.*, 1950) and hyaluronidase is inhibited by both (Dorfman *et al.*, 1947). Increased excretion of reducing steroids in response to salicylates has been demonstrated (Van Cauwenberge and Heusghem, 1951). Sayers (1950) suggested that salicylates exert their effect by promoting the utilization of adrenocortical hormones peripherally in the tissues, and that this leads to increased production of A.C.T.H. The pituitary does seem to be necessary, for Hetzel and Hine (1951) were unable to demonstrate either eosinopenia or depletion of ascorbic acid and cholesterol in the adrenals of hypophysectomized rats that were given salicylate, but obtained these responses in normal rats. Meade and Smith (1951) suggest only two points of difference in action between the hormones and salicylate: one is the effect on glycosuria in diabetic rats, and the other is the effect on the clotting-time. A temporary eosinopenia with A.C.T.H. and cortisone is now well known and occurs when salicylate is given (Roskam *et al.*, 1951).

Reid (1948) stressed the electrolyte changes that occur with salicylate treatment of rheumatic fever, and pointed out the danger of the increased plasma volume that is seen in the first few days of administration. We now know that this also occurs with hormone treatment. Cochran *et al.* (1950) observed an increase in body hair, abnormal

*The suggestion that corticogenic hypothyroidism is due to the inhibition of thyroid-stimulating hormone (T.S.H.) is contraindicated by the finding of Perry (1951). He showed in rats that after seven days' cortisone administration there was no change in the thyroid weight. Also, thyroxine, which depresses T.S.H. secretion, lowered the rate of I^{131} release from the thyroid, whereas high levels of cortical hormones had no such effect.

fat distribution, and a tendency to acne with salicylate treatment. We have seen red striae developing on the breasts of two girls, one receiving A.C.T.H. and the other receiving salicylate.

Role of A.C.T.H., Cortisone, and Salicylates

We all recognize that it is the carditis that needs to be eliminated if treatment is to be regarded as successful. May Wilson believes that patients who are given A.C.T.H. during the first days of illness are cured of their rheumatic fever (Wilson and Helper, 1951). She stated at the Second A.C.T.H. Conference that A.C.T.H. given "during the acute exudative inflammatory phase before there is irreversible damage results in termination of the acute rheumatic process" (*Proceedings of A.C.T.H. Conference*, p. 627). Other speakers at the conference stated that A.C.T.H. was not curative in their early cases. They pointed out that patients seen shortly after the illness began usually responded well to salicylate treatment, and implied that this was evidence against Dr. Wilson. All speakers were in agreement that cases of long duration showed only a suppression of the rheumatic process in response to treatment with cortisone and A.C.T.H.

Coburn (1943) believes that high and prolonged salicylate dosage is essential for the removal of clinical evidence of carditis and leads to a greatly reduced incidence of subsequent valvular disease. Satisfactory serum salicylate levels are often not maintained, however, because dosage is reduced on account of tinnitus or other toxic effect. The level fluctuates widely even on the same dosage, and it is not generally known that sodium bicarbonate, often prescribed with sodium salicylate, lowers the serum level (Smith *et al.*, 1946). We would stress, too, that the sodium salt should be avoided. For these reasons, and because of the natural severity of the disease in some patients, many cases of rheumatic fever are not relieved by salicylate therapy.

We have, to date, no conclusive evidence that hormone therapy is better than salicylates in reducing cardiac inflammation, but A.C.T.H. and cortisone do in fact suppress fever and nodules where salicylates have failed.

We started with 100 mg. of cortisone intramuscularly daily when treating children and adults. If given orally the dose should be increased by a fifth to obtain the same degree of response. Better initial suppression would be achieved by larger initial doses, and we should now give 300 mg. for a few days and then continue with 125 mg. as maintenance dosage. Severely ill patients should be watched for the increased plasma volume in the first days of treatment. The customary dose of A.C.T.H. is 25 mg. intramuscularly every six hours. If this is insufficient, 20 mg. every four hours will exert more effect than 30 mg. every six hours. Salicylate should be given in full dosage and should maintain a serum level above 30 mg. per 100 ml. The sodium salt is best avoided. As with hormone therapy, the diet should contain little sodium.

Conclusion

We believe it reasonable to hold as a working hypothesis that the chief pharmacological activity of salicylates is in some way related to the metabolism of corticosteroids. Similar clinical and biochemical changes occur with the administration of salicylates, cortisone, and A.C.T.H. The aim when any of these substances is used in the treatment of rheumatic fever should be to achieve a rapid resolution of symptoms, a normal cardiac rate, a fall of the E.S.R. to normal, and a steady rise of haemoglobin. These changes will depend mostly on a satisfactory dosage. These features should be present for at least four to six weeks before treatment is discontinued. Relapse will then occur only if the rheumatic state should still exist in the patient; but false relapse due to temporary pituitary or adrenal insufficiency must be recognized as such when hormone dosage is reduced, and will then last no more than a few days. A.C.T.H. and cortisone seem to be more certain in action

than salicylates; that they are also more potent is suggested by the greater ability to induce Cushing-like effects. We believe that A.C.T.H. and cortisone will prove to be the best forms of treatment for most cases of rheumatic fever. Salicylates should be adequate as routine treatment, especially in early cases, and this is important while the cost of the hormones remains high. We do not yet know to what extent the morbid anatomical changes of rheumatic disease are reversed by treatment, and comparison between hormones and salicylate is difficult. Whether or not the incidence or severity of valvular disease is curtailed has yet to be determined.

Summary

Four children severely ill with rheumatic fever and pericarditis showed a prompt improvement when treated with cortisone. The duration of treatment varied from 44 to 120 days. With reduction of dosage the signs and symptoms of rheumatic activity recurred. There was no increase of disability in the two patients who had previous rheumatic valvular disease. In the other two patients it was their first attack. One was left without apparent heart damage; the other appeared to be fully recovered, but shortly after relapsed following a throat infection. This patient responded to a course of A.C.T.H., but a systolic murmur persists.

In all of these cases some clinical features of adrenocortical excess were observed. Weekly examination of the serum cholesterol showed a constant rise during administration of either hormone. Four patients were then treated with high dosage of salicylates, and clinical and biochemical changes, similar to those in the hormone-treated cases, were noted. In particular, mention must be made of the development of red striae on the breasts of two girls, one treated with A.C.T.H. and the other with salicylates. The administration of salicylate was found to lead to an initial fall of the serum cholesterol followed by a rise which was maintained throughout the treatment. This initial fall resembles that seen when A.C.T.H. is given.

It was concluded that it was justifiable to hold as a working hypothesis that salicylates exert their pharmacological activity by engendering adrenocortical excess. When salicylate, A.C.T.H., and cortisone are administered, rheumatic activity is suppressed. The criteria of dosage and of duration of treatment are the same when any of these substances is used.

ADDENDUM

We have observed the serum cholesterol in two further cases of acute rheumatism treated with salicylates. The cholesterol figures, on the days of treatment shown, conform to the pattern described above.

Day:	Serum Cholesterol (mg. per 100 ml.)													
	1	2	3	4	5	6	7	14	21	28	35	42	49	56
Case 9	168	120	130	156	195	—	188	230	192	230	—	—	235	270
" 10	108	87	88	87	128	136	—	190	122	—	194	170	158	188

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RELATION OF ELECTROLYTE CHANGES AND ADRENOCORTICAL ACTIVITY TO PARALYTIC ILEUS

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There has been much speculation about the cause of paralytic ileus ever since Thomas Sydenham (1666) differentiated the condition which he referred to as "true ileus" from the "bastard ileus" caused by mechanical obstruction. Sydenham thought that "true ileus" was due to fever which brought about a "commotion of the blood" so that "acid and malignant humours are lodged in the stomach and in those parts of the intestinal canal that lie nearest to it." Other "commotions of the blood" have continued to enjoy recognition as possible causes of the condition now known as paralytic ileus, and in recent years the suggestion has been made that electrolyte deficiencies may be among the responsible agents.

It has been known for some time that hypertonic sodium chloride infusions stimulate vigorous peristalsis in experimental animals (Hotz, 1909) and in patients with

paralytic ileus (Hughson and Scarff, 1924). More recently, French authors (Robineau, 1933; Lévy and Nora, 1935, 1946) have attributed paralytic ileus to the low concentration of chloride observed in the plasma and in the blood cells in this condition, and have attempted to prevent the onset of ileus by the routine administration of large amounts (45–50 g.) of sodium chloride daily in the immediate post-operative period. Marriott (1947) has also suggested that chloride deficiency may be the cause of some cases of ileus, and Streeten (1950) has shown that the propulsive motility of actively contracting preparations of human intestine can be abolished by their immersion in fluid with a lowered chloride concentration similar to that which occurs in the plasma of patients with paralytic ileus.

Maddock (1939) found that post-operative hypochloræmia refractory to isotonic sodium chloride administration abated when the patients began to eat a normal diet. This observation prompted Ariel, Abels, Pack, and Rhoads (1943) to administer large amounts of protein orally and parenterally to patients with post-operative ileus associated with the same sodium-chloride-refractory hypochloræmia; their five patients all responded favourably. Randall, Habif, Lockwood, and Werner (1949) suggested that potassium deficiency was responsible for the syndrome described by Ariel *et al.* (1943), and hastened recovery by giving potassium solutions intravenously. Darrow (1950), too, stated that intestinal distension and paralytic ileus are among the results of potassium deficiency.

The clinical suggestion that potassium deficiency may cause paralytic ileus is considerably strengthened by a rapidly accumulating body of experimental evidence. Winter, Hoff, and Dso (1949) showed that the tone and motility of the whole gastro-intestinal tract were reduced, and the passage of a barium meal retarded, in rats made deficient of potassium either by repeated injections of deoxycortone or by lowering potassium intake. Webster, Henrikson, and Currie (1950) reported similar results in rats, but found that in dogs with potassium deficiency there was only a slight reduction in the strength and rate of rhythmical contractions of the alimentary tract. Streeten and Vaughan Williams (1952) have found that fluid transport by intestinal loops can be abolished in dogs by progressive sodium chloride depletion. The intestinal paralysis came on only when, as a result of chloride deficiency and adrenocortical stimulation, a rapid loss of cellular potassium took place, causing a sudden increase in the plasma concentration of this ion. When the propulsive motility of intestinal segments was abolished *in vitro* by reducing the sodium chloride content of the surrounding fluid, it was possible to demonstrate a large fall in the potassium concentration of the bowel wall and a consequent rise in the concentration of this ion in the surrounding fluid. In other unpublished experiments it was not possible to paralyse dog intestine by reducing the potassium concentration of the external medium to as low as 5 mg./100 ml. for periods of over an hour.

The recent evidence is therefore consistent with the view that intracellular, though not extracellular, potassium deficiency can cause paralysis of gastro-intestinal motility both *in vivo* and *in vitro*. The present study was undertaken in an attempt to discover the relation of potassium and chloride deficiency and adrenal cortical hyperactivity to the development of paralytic ileus in man.

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