A.C.T.H. AND CORTISONE IN IDIOPATHIC THROMBOCYTOPENIC AND SCHÖNLEIN-HENOCH (ALLERGIC) PURPURA

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Several reports of the efficacy of A.C.T.H. and cortisone in idiopathic thrombocytopenic purpura and Schönlein-Henoch (allergic) purpura have been published. The results have been by no means consistent. The factors involved in their action have still to be clarified, and it is apparent that their precise status in the treatment of purpura has yet to be defined.

The following is a report of three cases of idiopathic thrombocytopenic purpura and a case of Schönlein-Henoch purpura treated with A.C.T.H. and/or cortisone. A brief review is included of reports so far available on the use of these hormones in haemorrhagic disorders.

Case 1

A girl aged 14 was admitted to Arbroath Infirmary on January 3, 1952, in an acute haemorrhagic state. Her periods had begun five months before admission, and during that time menstruation had been normal and regular. During the fortnight before admission there had been prolonged vaginal bleeding, epistaxis, and a tendency to bruise easily. There was no previous history of bleeding in the patient or her family, and no drugs had been taken recently. On admission she was severely exsanguinated, bleeding from nose, mouth, and vagina, and showing diffuse purpura and ecchymoses over her shins and feet. The spleen, which was not at first felt, later enlarged, and the tip became palpable a few days after admission. There was no lymphadenopathy. Blood examination on admission was as follows: Hb, 3.5 g.%; red cells, 1,980,000 per c.mm.; white cells, 9,900 per c.mm.; P.C.V., 15%; M.C.V., $76 \mu^3$; M.C.H.C., 35%; platelets, 70,000 per c.mm. A blood film showed a considerable number of polychromatophilic cells and a few normoblasts; a few myelocytes but no other primitive leucocytes were seen. Bleeding-time, 9 minutes; coagulation time (Lee and White), 9 minutes; Hess test, positive. Sternal puncture on January 4 showed a highly cellular reactive normoblastic marrow with numerous megakaryocytes. On these grounds a diagnosis of idiopathic thrombocytopenic purpura was made.

Despite transfusions of fresh blood—20 pints (11.4 litres) in 10 days—the haemorrhagic state continued, and on the fifth day after admission the bleeding-time had risen to 24 minutes. A.C.T.H., 25 mg. six-hourly, was begun on the seventh day, a total dosage of 375 mg. being given without clinical or haematological effect. On the eleventh day oral cortisone, 50 mg. twice daily, was started. A partial clinical response occurred, as shown by a lessening of blood loss, but the bleeding-time was still increased at 12–18 minutes and the platelet count remained low at 25,000–60,000. In view of this incomplete response, cortisone was stopped and splenectomy was carried out on the seventeenth day. This induced a satisfactory remission. Traces of bleeding from

the nose or vagina occurred for a few weeks after operation and then ceased completely. Some fall in the bleeding-time was noted as early as the evening of operation, when a reading of 9 minutes was found. A week after splenectomy this had fallen to 4 minutes, and subsequently values between 2 and $3\frac{1}{2}$ minutes were obtained. The platelets remained depressed for a week after splenectomy with counts ranging from 30,000 to 67,000 per c.mm. The count had risen to 210,000 per c.mm. two weeks after splenectomy and to 386,000 per c.mm. after three weeks. On her discharge from hospital on March 1 the blood showed: Hb, 9.8 g.%; red cells, 4,350,000 per c.mm.; white cells 5,500 per c.mm.; platelets, 500,000 per c.mm.; bleeding-time, 3 minutes; coagulation time, normal.

Comment.—In this patient A.C.T.H., 100 mg. daily, produced no effect. A partial remission, as evidenced by the reduced haemorrhage from the nose and vagina and the reduced rate of fall of haemoglobin, followed the administration of oral cortisone, 100 mg. daily. No change occurred in the bleeding-time or platelet count. Splenectomy induced a complete remission.

Case 2

A boy aged 5 was admitted to Arbroath Infirmary on January 16, 1952, with the history of continued bleeding from a tooth socket following extraction three weeks previously. During the same period there had been recurrent epistaxis. No previous abnormal bleeding had occurred in the patient or in the family, except in a female cousin who was said to be a "bleeder." No drugs had been taken before the onset of the illness. Physical examination showed a severe anaemia, with scattered petechiae and ecchymoses of the skin, and bleeding from a tooth socket and from the nose. The liver and spleen were not enlarged and there was no obvious lymphadenopathy. A blood examination resulted as follows: Hb, 5.5 g.%; red cells, 2,000,000 per c.mm.; white cells, 13,850 per c.mm. (neutrophils 53%, lymphocytes 35%, monocytes 5%, myelocytes 7%); platelets, 40,000 per c.mm.; nucleated red cells, 3 per 100 white cells; bleeding-time, 30 minutes; coagulation time (Lee and White), 4 minutes; Hess test, positive. An iliac marrow smear showed a highly cellular normoblastic marrow, while sections showed abundant megakaryocytes and promegakaryocytes and some increase in eosinophils. Leucopoeisis was slightly increased but normal. A diagnosis of idiopathic thrombocytopenic purpura was made.

Despite blood transfusions—6 pints (3.4 litres)—severe haemorrhage continued. Oral cortisone, 50–100 mg. daily, which was started on the sixth day after admission, produced no clinical improvement and no rise in the platelet count, which varied from 26,000 to 58,000 per c.mm.; the Hess test did, however, become negative and there was some fall in the bleeding-time. On the eleventh day the cortisone was stopped and splenectomy carried out. Following splenectomy there occurred a prompt and sudden fall in the bleeding-time, with cessation of all bleeding. Twenty-four hours after operation a transient but severe relapse occurred, with a recurrence of bleeding and a rise in bleeding-time. Thereafter progress was satisfactory, but the platelets did not begin to rise for three weeks, and normal figures were not reached until 28 days after splenectomy. On his discharge from hospital on February 28 the bleeding-time was 3 minutes and the Hb 11 g.%.

Comment.—In this patient oral cortisone, 50–100 mg. daily produced no improvement in the haemorrhagic state or in the platelet count. A slight fall in the bleeding-time coincided with the administration of cortisone, and the Hess test became negative.

Case 3

A woman aged 72 attended the blood clinic in Maryfield Hospital, Dundee, in April, 1952, with a complaint of a generalized petechial rash and scattered ecchymoses, beginning in January, 1952. Physical examination showed numerous petechiae and several ecchymoses, up to 2 in.

(5 cm.) in diameter and at all stages of resolution, on limbs and trunk, and one large mucous haemorrhage in the tongue, but was otherwise negative. Indeed, the patient was surprisingly fit and youthful in appearance. The spleen was not palpable. Investigation revealed all the haematological characters of idiopathic thrombocytopenic purpura, with a strikingly positive Hess test and no clot retraction in 24 hours. The initial platelet count was 30,000 per c.mm. and the bleeding-time over 35 minutes. At no stage was there significant anaemia, the initial Hb being 14 g.% and the red-cell count 4,500,000 per c.mm. The blood film was normal except for very scanty platelets, and the only marrow abnormality was a great excess of megakaryocytes, mostly immature, in the crusted fragments. Clotting-time and prothrombin concentration were normal. No drugs had been taken except ascorbic acid, administered without effect after the onset of symptoms, and there was nothing else of possible aetiological importance in the history. In spite of the patient's age, therefore, the diagnosis of idiopathic thrombocytopenic purpura was made.

After a control period of 14 days, during which symptoms and signs continued, treatment with A.C.T.H. was started; 40 mg. daily for three days followed by 80 mg. daily for seven days in divided six-hourly doses. By the fifth day of A.C.T.H., 80 mg. daily, the Hess test was negative, the bleeding-time had fallen to 8 minutes and the platelets numbered 45,000 per c.mm. On the seventh day bleeding-time was 15 minutes and platelets numbered 40,000. Treatment was then changed to oral cortisone, 25 mg. six-hourly, and within four days the response was complete, with a bleeding-time of 2 minutes and a platelet count of 250,000 per c.mm. Clot retraction became normal, and the marrow showed reduction in numbers of megakaryocytes. When the dose of cortisone was reduced, relapse of thrombocytopenia and bleeding-time occurred at once, and was well established within five days of stopping cortisone. On the ninth day without treatment the Hess test was also again positive. A second complete response took place on readministration of 100 mg. of oral cortisone daily, platelets reaching 370,000 per c.mm. in two days. The patient was discharged, being seen again two weeks after the second course of cortisone. Mild purpura had recurred, the bleeding-time was 17 minutes, and the platelets numbered 30,000 per c.mm.

Comment.—This patient showed partial response to A.C.T.H., 80 mg. daily, and reversal of all the features of the disease on two occasions with 100 mg. of oral cortisone daily.

Case 4

A girl aged 13 was admitted to the Royal Infirmary, Dundee, on March 20, 1952, with the complaint of a rash accompanied by abdominal pain, sickness, and loose offensive stools containing red blood during the previous week. Five weeks before this she had a sore inflamed throat, which was treated with penicillin. Following this she developed intermittent pain and swelling of the ankles and a rash confined mainly to the arms and legs. Her previous health had been good and there was no previous allergic history, either in the patient or in her family. She had undergone an operation for "obstruction of the intestine" when aged 5.

On examination she was listless, and complained of lower abdominal pain. A well-marked purpuric rash was present over the shoulders, arms, and legs, and only a few petechiae were seen on the chest, face, and limbs. Pustular lesions were present over both ankles and heels. The liver and spleen were not enlarged and there was no lymphadenopathy. The throat was red, but no exudate was present. The abdomen was tender in both iliac fossae, but no masses were felt. No abnormality was found in the heart or lungs. The stools contained red blood. Blood examination on admission gave the following results: Hb, 13.1 g.%; red cells, 4,700,000 per c.mm.; white cells, 9,200 per c.mm. (neutrophils 66%, lymphocytes 29%, monocytes 4%, eosinophils 1%); P.C.V., 37.5%; M.C.V., $89 \mu^3$; M.C.H.C., 35%; platelets, 520,000 per c.mm. A blood film showed no abnor-

malities in the red or white cells except for an occasional "irritation" lymphocyte. E.S.R., 18 mm. (Wintrobe); bleeding-time, $3\frac{1}{2}$ minutes; clotting-time, 5 minutes; Hess test, positive. Urine examination showed the presence of red blood cells, but no casts were seen. No intestinal pathogens were found on stool culture. *Staphylococcus pyogenes* and *Streptococcus viridans* were obtained from culture of a throat swab. The Widal reaction was negative.

A diagnosis of Schönlein-Henoch purpura was made and a small dose of A.C.T.H., 10 mg. twice daily, was started on March 26. A dramatic improvement occurred as early as 12 hours after treatment began; the abdominal pain and haemorrhage from the bowel stopped and the appetite returned. The intermittent pyrexia and tachycardia which had been present promptly disappeared with A.C.T.H. therapy and the purpura lessened, but the Hess test remained positive. After six days A.C.T.H. was stopped and a prompt relapse occurred, and there was again rapid improvement when the drug was restarted. The A.C.T.H. was replaced by oral cortisone, 12.5 mg. twice daily, on April 3 and no relapse occurred even when the cortisone was reduced to 12.5 mg. once daily. All drug treatment was stopped on April 9 and the patient was well when discharged from hospital on April 24. Since discharge her general condition has remained good, but small crops of petechiae have occurred and the Hess test has remained positive. There has been no recurrence of joint symptoms, abdominal pain, or intestinal haemorrhage.

Comment.—In this patient A.C.T.H., 10 mg. twice daily, produced a rapid improvement in the clinical condition with a disappearance of abdominal pain and intestinal haemorrhage and a lessening of the purpura. The Hess test remained positive. Oral cortisone, 12.5 mg. twice daily, maintained the improvement.

Discussion

During the last two years convincing evidence has accumulated that both A.C.T.H. and cortisone may increase capillary resistance, and also, according to the majority of reported studies, increase the platelet count and reduce the bleeding-time in idiopathic thrombocytopenia. In spite of this, reports of clinical trials of these hormones in purpuric syndromes have been by no means uniform, and neither the exact mode of action nor the type of case in which success may confidently be expected has yet been established. Robson and Duthie (1950) demonstrated an increase in capillary resistance in normal vessels after the application of various types of bodily stress. This increase is presumably mediated by adrenocortical stimulation as it follows the administration of A.C.T.H. They also reported response to short courses of A.C.T.H., including significant rises in platelets, in two patients with idiopathic thrombocytopenic purpura. Complete reversal of the haematological findings in this disease rapidly following the administration of A.C.T.H. or cortisone has been reported by Wintrobe (1950); by Bethell *et al.* (1951) in all seven patients treated; by Wightman (1951) in two cases; by Jacobson and Sohler (1952) in three cases; and by Evans and Liu (1951), who obtained two distinct responses in a severe case. On the other hand, Ragan (1951) found no change in the platelets in two patients who had relapsed after splenectomy with either cortisone or A.C.T.H., although the purpura was relieved; while of 10 patients treated in the M.R.C. investigation (1952) only five responded. Moreover, Spaet and Mednicoff (1951) quote unpublished negative results obtained by Dameshek and Stefanini in this disease.

The present report adds to the list one case (No. 3) which showed decrease of capillary fragility and purpura with A.C.T.H. without any effect, in the dosage used, on the thrombocytopenia; in another case (No. 2) oral cortisone had a slight similar effect, while in a third case no response occurred to A.C.T.H. and oral cortisone in doses of 100 mg. daily. One case (No. 3) responded completely to oral cortisone; there can be no doubt that remission was due to the hormone, as relapse rapidly followed its withdrawal, and

response to 100 mg. daily was again complete, with relapse following again on the second withdrawal.

The factors which determine success or failure with this treatment in thrombocytopenia are as yet far from clear. In some cases 100 mg. of A.C.T.H. daily has produced complete response. In other patients, such as Case 3 reported here and two cases described by Bethell *et al.*, A.C.T.H. produced improvement only in capillary resistance, while cortisone produced a complete response. A third group responded only symptomatically or not at all to both A.C.T.H. and cortisone. Dosage is probably important, as requirements may well vary widely from case to case. One case reported by Bethell *et al.* responded only when 300 mg. of cortisone was given daily, and the negative results in our Cases 1 and 2 may be due to inadequate dosage: the supply of cortisone was limited, however, and as these patients were seriously ill it was not advisable to delay splenectomy.

Bethell *et al.* suggest that patients failing to improve or relapsing after splenectomy, or those with megakaryocytic aplasia, will not respond to A.C.T.H. or cortisone (although the purpura may be improved symptomatically), and yet four cases are on record of response occurring in splenectomized patients who had relapsed (Bethell *et al.*, 1951; Evans and Liu, 1951; Jacobson and Sohler, 1952), so that presence or absence of the spleen can scarcely be a factor, unless the possibility of a hyperplastic spleniculus is admitted. Similarly, Wightman (1951) reported complete remission in one patient in whose marrow no megakaryocytes could be found. In general, however, successfully treated cases have shown megakaryocytic hyperplasia in the marrow.

So far there appears to be no report of successful use of these hormones in secondary or toxic thrombocytopenia, and Finch (1951) mentioned one failure in thrombocytopenia due to gold. However, two of the cases of allergic purpura described by Kugelmass (1951) had thrombocytopenia abolished by cortisone, and Evans and Liu ascribe the action of cortisone and A.C.T.H. in thrombocytopenia to the correction of an abnormal immunological response. In support of this explanation Evans and Liu cite evidence presented in the paper of Evans *et al.* (1951) for antithrombocyte activity in the serum in idiopathic thrombocytopenic purpura and for the aetiological relationship between this disease and acquired haemolytic anaemia. An actual thrombocytopenic factor, active in normal subjects, has been found by Harrington *et al.* (1951) in the serum of patients with thrombocytopenic purpura. Direct evidence for the effect of cortisone in relieving thrombocytopenic purpura artificially induced in rats by injection of antiplatelet serum was sought by Spaet and Mednicoff (1951), but with negative results. These authors favour the view that cortisone, when it acts in thrombocytopenia, does so by depressing antibody formation.

The duration of remissions in idiopathic thrombocytopenic purpura induced by cortisone and A.C.T.H. has in general been brief, but in some of the reported cases has lasted several months. The problem of maintenance dosage is discussed by Evans and Liu, who kept a patient "symptom-free" with 25 mg. of A.C.T.H. daily "in alternate weeks."

The Schönlein-Henoch syndrome is acknowledged to be an allergic disease, and our fourth patient was a girl of 13 who responded rapidly and completely to A.C.T.H. and cortisone. A feature of this case was the small dose of A.C.T.H. and cortisone (10-12.5 mg. daily) which prevented a relapse occurring. The weight of evidence at present supports the efficacy of A.C.T.H. and cortisone in this condition, and successes have been described by the following: Levinson *et al.* (1951) found a rapid response to 100 mg. of A.C.T.H. daily in a girl aged 15, but no effect on the renal manifestations; Morelli *et al.* (1951) described rapid improvement in a boy aged 8 with 30 mg. of A.C.T.H. daily, including improvement in the urinary findings; Portillo *et al.* (1951) described a dramatic response to 75 mg. daily in a girl aged 11 who was seriously ill after a control period in which

all the symptoms had worsened; Kugelmass (1951) recorded four prompt responses in children aged 9-15 to cortisone, 200 mg. initially, followed by 100 mg. daily; and Stefanini *et al.* (1950), whose case showed a more delayed response (six days) with a dose of 15 mg. A.C.T.H. daily. On the other hand, Woolley (1952) found no response to 60 mg. of A.C.T.H. daily in a boy aged 3½, but his opinion that further use of the hormone in this condition is not justified would appear to be untenable in face of the evidence so far available.

Conclusions

There is experimental and clinical evidence that A.C.T.H. and cortisone can enhance capillary resistance and improve the symptom of purpura, both in the presence and in the absence of thrombocytopenia, and whether the latter, if present, is affected by the hormones or not.

A.C.T.H. and cortisone have been effective in reversing the haematological changes in idiopathic thrombocytopenic purpura in most reported studies, but the mode of action and the factors determining response are still obscure, and further studies are necessary. Cortisone has on the whole been more effective than A.C.T.H. in this condition. We concur with the view of Jacobson and Sohler (1952) that in idiopathic thrombocytopenic purpura the trial of A.C.T.H. or cortisone is of practical value under two conditions—as a preparation for splenectomy, and to tide a patient over a critical bleeding episode.

A.C.T.H. and cortisone have proved efficacious in the great majority of reported cases of Schönlein-Henoch purpura, and their use is justified, especially in severe cases, though once again more extensive observations are required.

In purpuric states, oral cortisone is probably preferable, as repeated injections may give rise to haematomata.

Summary

Three cases of idiopathic thrombocytopenic purpura treated with cortisone and A.C.T.H. are described. One showed partial response to A.C.T.H. and complete response to oral cortisone, 100 mg. daily. Another showed no response to A.C.T.H. and a doubtful response to oral cortisone in the same dosage. The other case showed no response to both A.C.T.H. and cortisone. These two latter cases responded to splenectomy.

One case is described of Schönlein-Henoch purpura which responded dramatically to small doses of A.C.T.H. and oral cortisone.

The literature relating to the use of A.C.T.H. and cortisone in these conditions is briefly reviewed.

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