CORTISONE AND ITS ANALOGUES IN HAEMATOLOGY

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The influence of adrenal cortical secretion on blood elements was first noted in mice by Dougherty and White (1943) who showed that a single injection of pituitary adrenocortical hormone produced an absolute lymphopenia with a relative and absolute neutrophilia, and an increase in the numbers of erythrocytes and haemoglobin content.

Hills, Forsham and Finch (1948) demonstrated the influence of ACTH on circulating leucocytes in man. Thorn et al. (1948) showed the relationship between leucocyte numbers and adrenal activity, and Hench et al. (1949) in the first clinical trial of Compound E (or cortisone) on patients with rheumatoid arthritis, reported a concomitant increase in haemoglobin content and erythrocyte count during the course of therapy. It was apparent that there was good rationale for the use of cortisone and ACTH in blood diseases, and Farber et al. (1950) recorded a good response to ACTH in a five-year-old child with acute leukaemia. Results of subsequent applications were reviewed by Wintrobe et al. (1951).

Several analogues of cortisone are now available. Their relative potencies and advantages are described elsewhere in this Journal. In the haematological disorders to be discussed, cortisone or any of the related products in an equivalent dose, can, as a rule, be used with equal effectiveness.

The effects of adrenocorticosteroids on haemopoietic function occur by several possible mechanisms which are not fully understood.

Possible Mechanism of Effects

Eosinopenia:
Inhibition of production or release of eosinophils from the bone marrow.
Sequestration of eosinophils in spleen and/or lung.
Destruction of eosinophils in peripheral blood.

Erythropoiesis, Granulopoiesis:
Bone marrow stimulus.

Lymphopenia:
Involution of lymphoid tissue. This occurs in fixed lymphoid tissue of thymus and lymph nodes (in which the germ centres may disappear) and also in the peripheral blood. There is a similar, though temporary, effect on the lymphoid cells of lymphosarcoma and chronic lymphatic leukaemia.

Depression of Antibody Production:
Secondary to involution of lymphoid tissue.

Control of Hypersplenism:
Direct control on splenic activity by adrenal cortex.

Therapeutic trials with cortisone and its derivatives and ACTH on haematological disorders have met with varying degrees of success. In some groups of conditions steroids are firmly established as the treatment of choice, either alone or in combination with other methods of treatment, and this article reviews current thoughts on the subject.

Idiopathic Thrombocytopenic Purpura
Steroids act both by improving capillary resistance and by increasing platelet response. These actions are unrelated, and there may be a satisfactory vascular response without any change in the thrombocytopenia. The vascular response occurs within 2 to 10 days, preceding the platelet response, which usually occurs on the 6th to 11th day. Response to steroid is less satisfactory in the chronic phase than in the acute phase, with little rise in platelets, although there may be a satisfactory vascular response, indicated by a normal capillary fragility test, normal bleeding time, and remission of bleeding. Thus, even if the effect is temporary, steroids are of value in controlling bleeding, in order to tide over the patient until there is spontaneous remission, or until splenectomy can be carried out unhurriedly as an elective procedure with minimal blood loss. It
may also be of value in postsplenectomy cases, when the operation has failed to control the bleeding, or has produced an incomplete remission. There is no evidence that steroid therapy has any adverse effect on the response to subsequent splenectomy nor on wound healing. Failure to respond to the hormones is no gauge of the effect of splenectomy.

Davidson et al. (1952), in an investigation of 14 patients, found that with steroids alone only three were cured and a further three obtained temporary relief. Robson (1954), however, reviewed 103 cases from his own and other series, and found that in two-thirds of the cases not subjected to splenectomy, hormonal treatment controlled or diminished haemorrhagic manifestations.

Thus, the treatment of choice should be:

**Acute ITP (Less than three months’ duration):**

Initial dose of 150 units of ACTH or 150 to 300 mg. of cortisone daily, reducing the dose after remission to the smallest dose which maintains remission. Response is judged by decreasing capillary fragility and increasing platelet counts. If there has been platelet response, treatment should be continued for several months, but there is no point in continuing treatment beyond ten days if the patient fails to respond.

**Chronic ITP:**

Pre-operatively, 25 to 75 units ACTH, or 75 to 250 mg. cortisone daily for three days prior to surgery, tapering off this treatment in three subsequent days.

**Secondary Thrombocytopenia**

In this mixed group, the thrombocytopenia which occurs in relation to hypersplenism benefits from steroid treatment, which should be given in dosages of the same order as in acute idiopathic thrombocytopenic purpura.

Drug-induced thrombocytopenia was reported to respond favourably to high doses of steroids in the 2nd report of the M.R.C. Panel (1953). However, Thompson et al. (1954) reported no response to ACTH in two cases of thrombocytopenia secondary to gold therapy.

**Thrombotic Thrombocytopenic Purpura**

The histological appearance in this uncommon condition suggest a relationship to the collagen group of diseases. The use of steroids has been reported by Meacham et al. (1951) who induced a transient remission in one case, but Gendel et al. (1952), Adelson et al. (1954) and Marey et al. (1956) have reported cases who have failed to respond to large doses of cortisone and ACTH.

**Capillary Defects**

Early reports of the results of steroid therapy in Henoch-Schonlein disease were disappointing and in their 3rd report the M.R.C. Panel (1955) found that of eight cases classified broadly as non-thrombocytopenic purpura, six failed to respond to adequate doses of ACTH over a period of 12 to 20 days. Wald and Kissin (1955) found that in a patient in whom hereditary purpura simplex and Henoch-Schonlein syndrome co-existed, treatment with a combination of ACTH and antihistamines produced a good response. Nabarro et al. (1955) treated a patient successfully with prednisone; Stefanini and Martino (1956) reported that prednisone was especially effective in the management of acute anaphylactoid purpura and 'vascular pseudohaemophilia,' Cohen (1957) reported that in a patient with severe Henoch-Schonlein purpura cortisone in a daily dose of 200 mg. failed to have any effect whereas 40 mg. of prednisolone daily produced a dramatic remission and this was maintained with a daily dose of 15 mg.

**Coagulation Mechanism**

Cosgriff et al. (1950) and later Godowski (1951) reported that cortisone caused a decrease in coagulation time. Eisenmenger et al. (1952) studying this phenomenon in a series of patients with cirrhosis found no alteration in prothrombin, antithrombin, fibrinogen or platelet activity. The coagulation time decrease appears to be due to an antiheparin effect of the steroids. This has no therapeutic application in the control of coagulation defects but may be of significance in the production of thromboses. Eisenmenger records the development of portal thromboses in three of his patients with cirrhosis during treatment with ACTH. Patients on anticoagulant therapy and steroids may still develop thrombi despite apparent adequate anticoagulant dosage with a low level of blood ‘prothrombin’; such patients should be controlled on heparin as well as by dicoumarol.

**Haemolytic Anaemias**

The introduction of cortisone and ACTH has markedly influenced the management of acquired haemolytic anaemias due to auto-antibodies in a large proportion of which the haemolytic process can be interrupted and the anaemia relieved.

One of the actions of the steroids is the reduction of antibody concentrations in the serum but this is only one of several mechanisms of steroid action. Increased erythropoiesis, inhibition of erythrophagocytosis, prevention of antibody-antigen action by some blocking mechanism and inhibition of cell permeability play some part in the
mechanism. In their second report the M.R.C. Panel (1953) recorded only moderate effectiveness in the treatment of acquired haemolytic anaemias, but as Dameshek (1952) pointed out, the doses had been low and in the third report of the M.R.C. Panel (1955) after doses of the steroids had been increased, there appeared to be excellent response, with only two out of ten patients failing to respond at all, while five patients went into complete remission.

Dacie (1954) reviewed the literature on the use of steroids in haemolytic anaemias, and recorded his findings in his own group of patients. Clinical and haematological remission (though without necessarily any alteration in antibody titre) were observed in both idiopathic acquired haemolytic anaemia of the warm antibody and of the cold antibody type. In secondary haemolytic anaemia associated with auto-antibodies there may also be temporary haematological and clinical remission.

If the patients respond at all this will be shown within two weeks of the commencement of adequate treatment. Dosage required varies and it is emphasized that in an initial course treatment to the limit of the patient's tolerance may be necessary to control the haemolytic process. Starting with a daily dose of 300 to 400 mg. of cortisone, after response it is possible to cut down the dose to the minimal amount necessary to maintain the patient with a haemoglobin level of 10 gm. per cent. Impending relapse is indicated by a slight fall in the erythrocyte count and haemoglobin level, with a rising reticulocyte count (Fig. 1). Meyer and Ritz (1954) have suggested that as the adrenal may produce hormones other than cortisone which might be capable of supressing haemolytic activity, ACTH may be of value in inducing remission when cortisone alone has failed; de Gruchy (1954) has found similar results in four patients. Conversely, patients may respond favourably to cortisone when ACTH had proved to be ineffective. Dameshek and Komninos (1956) have shown that on occasions prednisone has proved effective when cortisone has failed. Splenectomy is a well-recognized method of treatment of acquired haemolytic anaemia. Steroids may be used for as long a time as possible before splenectomy is recommended in order to give the steroid therapy adequate trial.

As Dameshek and Komninos point out, the failure of steroid therapy should not be accepted until various preparations have been tried and if possible by various routes of administration. It is worth remembering that when there has been no response to an initial course of cortisone, and splenectomy has failed to produce an adequate response, a further course of cortisone, after splenectomy, may produce a satisfactory remission.

In haemolytic disease of the newborn steroids therapy to the mother during pregnancy does not
are not the hoped-for panacea but they do fill an important place in the management of leukaemia.

**Acute Leukaemia**

*Lymphoblastic Leukaemia.* Maximal effect, often with dramatic improvement, is found in lymphoblastic leukaemia. Complete remissions have been reported in 82 per cent. of cases in children by Fessas *et al.* (1954) and equally favourable have been the findings of Wintrobe (1956). Adults, however, are relatively refractory to ACTH and cortisone (Hayhoe and Whitby, 1955). The M.R.C. Panel (1954) reported good remissions in 70 per cent. of children and in a smaller number of adults resistance to the antimetabolite begins to develop (Fig. 2).

In an adequate remission the leucocyte count falls to normal range in three to seven days with a decrease in the percentage of blasts. After the first week the platelets increase and after the second week the haemoglobin rises. At the end of four to six weeks the bone marrow is likely to be normal. The duration of the remission varies greatly from weeks to several months. After relapse, a second remission on steroids will be less complete or may not develop at all. Leucopenia is not an absolute contra-indication to steroid therapy.

**Myeloblastic and Monoblastic Leukaemia**

In myeloblastic and monoblastic leukaemia steroids not only fail to produce remission but have been shown to accelerate the leukaemic process, often converting an aleukaemic phase into a frankly leukaemic process at an alarmingly rapid rate (Robson, 1954) (Fig. 3). Bjorckman (1956) has suggested that this might even be of use as a diagnostic test in differentiating cell types in acute leukaemia, but this is a somewhat drastic manoeuvre. Certainly, development of a frankly leukaemic picture should be an indication to take the patient off steroid therapy.

There have been scanty reports on the use of steroids in the rare condition of eosinophilic leukaemia. Davidson *et al.* (1952) found no beneficial result in a one-year-old infant, although previously Donohue *et al.* (1950) had found a good initial response in a seven-year-old boy, who had thirteen weeks' remission after the first two courses of treatment.

**Chronic Leukaemia**

In chronic lymphatic leukaemia cortisone gives temporary benefit which is less well sustained than that from X-ray therapy, but cortisone is of especial value in cases where there is a thrombocytopenia or an associated haemolytic anaemia. The
Steroids in the treatment of these complications has been discussed above.

In chronic myeloid leukaemia steroid therapy does not produce remissions and may even accelerate the leukaemic process.

Reticuloses

Steroids are not the treatment of choice but may be of some value in Hodgkin's disease and in lymphosarcoma when there is an associated haemolytic anaemia. Alpert et al. (1951) reported that the undesirable side-effects of anorexia, nausea and vomiting as a result of nitrogen mustard, are minimized when the drug is combined with cortisone. Hochman and Ickowicz (1954) reported that in eleven cases of lymphoblastic disease (lymphosarcoma, reticulosisarcoma and giant follicle lymphoma) and Hodgkin's disease, in which resistance had developed to nitrogen mustard, remissions of 1 to 4 months' duration followed when the nitrogen mustard was administered with small doses of cortisone. This may be partly explained by the suggestion that nitrogen mustard acts by stimulation of adrenal cortical secretion and that resistance develops because of an exhaustion of this secretion. Nabarro et al. (1955) found that prednisone alone in a dose of 30 mg. daily produced a satisfactory remission in a patient with Hodgkin's disease.

Multiple Myeloma

Thorn et al. (1950) reported that a patient improved as a result of treatment with ACTH. Clinical improvement was associated with a fall in globulins and the disappearance of plasmablasts from the bone marrow. Others have been less enthusiastic, though Adams et al. (1954) reported symptomatic relief, at least, in most patients and an occasional prolonged remission.

Volpé et al. (1956) reviewed the condition of essential cryoglobulinaemia. ACTH treatment resulted in clinical benefit in several cases but only in some of them did the concentration of cryoglobulin fall parallel with the degree of clinical improvement. However, Wirtschafter et al. (1956) observed the association between the disappearance of the cryoglobulin and clinical remissions following treatment with cortisone whereas the withdrawal of cortisone was immediately followed by the reappearance of the abnormal protein and clinical relapse.

In macroglobulinaemia steroids may produce a temporary remission but on the whole they have little effect either on the course of the disease or on the abnormal protein present. (Mackay et al., 1956; Laurin et al., 1957).

Infectious Mononucleosis

Prompt improvement of severe glandular fever, especially of the anginose type, has been reported following treatment with steroids (Mandel et al., 1955; Bender and Houghton, 1953; Brutsche and Naegle, 1954; Doran and Weisberger, 1953). In Mandel's patient intravenous ACTH brought about a rapid decrease in the signs and symptoms. Improvement was clinically obvious within sixteen hours and the pharyngeal inflammation promptly subsided—before this a tracheotomy had been indicated. However, abnormal cells were present in the peripheral blood even after all the abnormal physical signs had disappeared. Steroids were reported to have been of dramatic value in cases of infectious mononucleosis complicated by thrombocytopenia (Frenkel et al., 1956) or by meningencephalitis (Copeman, 1956).

Aplastic and Refractory Anaemias

As mentioned previously, steroids stimulate erythropoiesis and this appears to be the basis for the slight improvement sometimes seen in cases of secondary hypoplastic anaemia as a result of steroid therapy. However, little can be done to stimulate an aplastic marrow into activity. In primary refractory anaemia steroid therapy has
more frequently been followed by haematological improvement which is characterized by reticulocytosis in the blood, increased iron utilization and the conversion of a hypoplastic bone marrow to normal. Steroid therapy appears to be equally effective in cases where the anaemia is associated with a normal bone marrow (Loe et al., 1953; Hill and Hunter, 1951).

Agranulocytosis

Rapid improvement has been noted in cases of agranulocytosis due to amiodopyrine (Hart et al., 1952; Durant, et al., 1955), tapazole treatment of hyperthyroidism (Levine and Rosenberg, 1954), sulphanilazine (McMillan, 1951), propylthiouracil (Murray et al., 1957) and other factors (Caldwell et al., 1950; Virkkunen, 1953; M.R.C. Panel, 1953). However, it is difficult to assess the role of steroids in many of these cases, as often withdrawal of the offending drug will result in a natural remission.

Hypersplenism

In primary hypersplenism steroids have been shown to produce clinical benefit and haematological response with restoration to normal of the platelets and the neutrophil count (Bethell et al., 1951). There does not appear to be any correlation between the effect of steroid therapy and response to splenectomy.

In secondary hypersplenism steroids do not appear to have any beneficial effect on the blood disorder.

Conclusion

Table 1 indicates the blood disorders in which steroids are the treatment of choice or at least serve a purpose. Their effectiveness can be assessed only after adequate doses have been administered for an adequate length of time. In adults treatment should be commenced with a daily dose of 300 to 400 mg. of cortisone, or approximately one quarter the dose of prednisone or prednisolone or 200 units of ACTH. If benefit results this is shown within a fortnight. If one steroid has not been effective others should be used by various routes of administration before this form of therapy is discarded.

Steroids are no panacea but they are of definite value in certain blood diseases, especially when their use is integrated with other forms of treatment.

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**Table 1**

**USE OF STEROIDS IN BLOOD DISORDERS**

**Maximum Value**

- Acute idiopathic thrombocytopenia purpura.
- Acquired (auto-immune) haemolytic anaemia (idiopathic or secondary).
- Lymphoblastic leukaemia.
- Severe infectious mononucleosis.

**Possible Value**

- Chronic idiopathic thrombocytopenia purpura.
- Henoch-Schönlein disease.
- Pernicious anaemia.
- Chronic lymphatic leukaemia.
- Reticuloses (including Hodgkin’s disease).
- Multiple myelomatosis.
- Refractory anaemia.
- Hypoplastic anaemia.
- Agranulocytosis.
- Primary hypersplenism.

**Little or No Value**

- Thrombotic thrombocytopenia purpura.
- Congenital haemolytic anaemias.
- Paroxysmal nocturnal haemoglobinuria.
- *Toxic* haemolytic anaemias.
- *Agranulocytosis foetalis.*
- *Secondary* thrombocytopenia.
- Secondary hypersplenism.
- *Good effect* has been reported in some cases.

**Probably contra-indicated**

- Monoblastic leukaemia.
- Myeloblastic leukaemia.
- Chronic myeloid leukaemia.

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