returned quickly to previous levels after the course was completed. In these six cases of rheumatoid arthritis, and in two cases of ankylosing spondylitis, the correlation between capillary resistance and eosinophil counts was fairly close.

The two cases of disseminated lupus erythematosus provide an instructive comparison. In one case a definite rise in capillary resistance was recorded after the administration of A.C.T.H. in a dosage which resulted in a decided clinical remission and a depression of eosinophils. In the second case, however, no such increase in resistance was recorded, clinical response to A.C.T.H. was poor, and the progressive deterioration was reflected by the falling capillary resistance. Since no eosinophils were found at any time in the peripheral blood in this case, the capillary resistance findings were of great value as an index of the lack of response to A.C.T.H.

The results in the two cases of thrombocytopenic purpura are of interest. It is noteworthy that capillary resistance rises in response to A.C.T.H. in this condition where the capillaries are believed to be abnormal. The moderate increase in platelets which was found to follow this increased resistance occurred at about the same time interval as the maximum thrombocytosis observed after splenectomy. While it would be unwise to draw more than tentative conclusions from such limited experience, definite clinical remission was induced by A.C.T.H. on three occasions in these two cases. Further study of the effects of A.C.T.H. in this and similar conditions would appear to be indicated.

It seems likely that the increase in capillary resistance which has been found to follow the administration of A.C.T.H., adrenaline, and insulin is due to adrenocortical activity. Such activity would account also for the changes in resistance which follow tissue damage and bodily stress. It is suggested that the measurement of capillary resistance provides a fairly simple and rapid method of following the response to A.C.T.H. or to substances which might be expected to have a similar effect.

Summary

It has been observed that an increase in capillary resistance, as measured by a negative-pressure method, occurs after the infliction of various types of tissue damage and after the application of various forms of bodily stress.

The results obtained suggest that this rise in resistance might be due to adrenocortical stimulation by the release of endogenous adrenaline or some similar mechanism.

Patients receiving adrenocorticotrophic hormone (A.C.T.H.) have been studied and the predicted increase in capillary resistance observed. The features of this response are described.

These observations led to the study of the effects of A.C.T.H. in two cases of idiopathic thrombocytopenic purpura; the results are described. Definite clinical remission was induced on three occasions.

It is suggested that capillary resistance estimations may be used in the measurement of the response to stimulation of the adrenal cortex.

Gratitude is expressed to Drs. E. B. French and A. G. S. Hill for much valuable assistance. We wish to thank Professor L. S. P. Davidson for helpful criticism and advice.

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THREE CASES OF SEVERE BURN TREATED WITH CORTISONE*

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In a former study (Crassweller, Farmer, and Franks, 1950), experimental evidence was presented suggesting that the mortality of experimentally burned mice was reduced by the administration of urinary extract fractions such as are known to contain the cortisone-active material. It thus seemed justifiable to consider giving cortisone in the treatment of severe clinical burns. In this paper three cases of severe burn are presented in which routine burn-therapy was supplemented by the administration of cortisone acetate in varying amounts. One case of 70% burn in an adult has done well. The other two patients (both children) died—one, however, 24 days after the burn and following a most promising early clinical response.

In reporting surface area of burns the modification of Berkow's formula (Lund and Browder, 1944) was used. Simple erythema has not been included.

As routine treatment all received occlusive pressure-dressings with light plaster casts. In Case 1 the burned surface was covered with aluminium foil (Brown, Farmer, and Franks, 1948), while in the other two vaselined gauze was used. Fluid requirements were maintained intravenously and by mouth in all cases.

Case 1

A well-nourished male child aged 23 months was admitted to the Hospital for Sick Children, Toronto, on June 8, 1950, in a moribund condition. He had suffered second-degree burns due to scalding, involving approximately 55% of his body-surface, including the legs, thighs, genitalia, and lower two-thirds of the trunk.

Treatment was started within one hour after the accident. To combat severe shock, 250 ml. of plasma was syringed at once into the radial artery. This resulted in an immediate return

*This work was carried out through a grant-in-aid supplied through the Defence Research Board of Canada.

to consciousness. 150 mg. cortisone acetate was administered intramuscularly at this time. In addition to the immediate shock therapy, plasma and normal saline were given intravenously to control haemoconcentration throughout the next few days. The haemoglobin fell on the third day to 7.2 g. per 100 ml., after which 500 ml. of whole blood was given. Daily injections of cortisone were continued to a total of 450 mg. (Fig. 3). In addition, 400,000 units of penicillin were given intramuscularly daily.

Considering his severe burn the child appeared to be doing well clinically, although his urinary output was small and bloody for the first 36 hours. On reduction of protein intake while fluids (glucose and saline) were maintained, his output suddenly increased and his urine became clear. Despite this turn and a normal non-protein nitrogen, he became comatose, with generalized twitchings and mounting fever at the end of the second day. On the third day his condition improved, with return of consciousness and good voluntary oral intake. However, at the end of the fifth day he lapsed into coma and died in respiratory failure with twitchings and hyperpyrexia.

Necropsy failed to reveal any significant findings apart from the burn. The adrenal glands contained adequate sudanophilic material.

Case 2

A girl aged 7 years was admitted to the Hospital for Sick Children, Toronto, on May 28, 1950, showing no evidence of shock other than rapid pulse and thirst. She had suffered flame burns to the extent of 30% of her body surface, involving the dorsum and left side of the trunk, the left arm, and left thigh. About one-third of the damaged area had second-degree burns and the remainder third-degree burns.

Treatment was begun 45 minutes after the accident. Haemoconcentration was controlled by the administration of 5,420 ml. of plasma in the first three days. Oral fluid intake was good throughout, as was also the calorie intake. She received penicillin, 400,000 units daily, beginning on admission.

On the first day the patient was bright and co-operative, but on the second day she began to appear ill, with a rising temperature and increasing pulse and respiratory rates (Fig. 1). Cortisone acetate 100 mg. was administered intramuscularly at this time and continued daily until the eighth day (Fig. 3). The temperature dropped and she remained remarkably well clinically. Dressings were changed on the tenth day. There was complete healing of the second-degree areas. Separation of slough was progressing normally. The dressings were heavily

contaminated with *Ps. pyocyanea*. From the eleventh day her condition deteriorated; she had a slowly rising and swinging temperature and showed signs of toxicity suggestive of a septicaemia. Blood cultures were negative. From the twelfth to twenty-second days sulphadiazine and streptomycin were given, with no apparent benefit. Her burned surfaces were examined with the hope of finding a localized focus of infection, but none was found. Granulations were well formed and appeared healthy. She received aureomycin from the twenty-third day. She became comatose and cyanotic, with a rising temperature which terminally reached 107° F. (41.7° C.). Death ensued with respiratory failure on the twenty-fourth day.

On removal of the dressings at necropsy a red macular rash was found over the abdomen and buttocks which had not been present 24 hours previously. The burned surface and dressings were heavily contaminated with *Ps. pyocyanea*, and this organism grew profusely in the culture of heart blood collected at necropsy. Since no other focus of infection was found, it is presumed that she died with a *Ps. pyocyanea* infection.

Case 3

A strong wiry man aged 21 was admitted to Victoria Hospital, London, Ontario, on May 8, 1950, suffering from severe flash burns sustained while working with high-tension wires. There were burns of most of the trunk, face, and neck, most of the left arm, and of the right arm to the elbow. The pubic hair and all the hair of the legs were singed, and there were burns of less intensity over these areas. The overall area of burn, excluding simple erythema, was estimated to be 70%. The total area of third-degree burn was estimated to be 15% of the body surface.

The face and neck were excluded from the occlusive pressure-dressings and were treated with penicillin cream. During the first 90 hours the patient required 24,750 ml. of plasma (Fig. 2) to maintain normal haemoglobin concentration. In addition he received 900 ml. of whole blood and 2,000 ml. of Ringer-lactate solution. He took fluids well by mouth throughout and received high-protein drinks from the second day on.

The patient was seen in consultation on the third day and cortisone therapy was suggested. This phase of the treatment was supervised by Dr. H. McAlpine. Daily cortisone injections were started on the fourth day (Fig. 3) and discontinued on the twenty-seventh day, following a total dose of 2,750 mg. 50,000 units of penicillin were administered intramuscularly every three hours. The patient remained well throughout and showed none of the stigmata of the so-called toxic phase.

Skin grafts were performed on the twenty-sixth, thirty-third, and fortieth days; all of these were successful. Because of the limited undamaged skin available, stamp grafts were used so as to cover a greater area. At the time of writing (seventieth day) the patient is still in hospital awaiting grafting of residual areas.

Discussion

The first patient (Case 1), according to the tables of mortality probabilities in burns prepared by Bull and Squire (1949), had less than a 40% chance of survival. He received a total of 450 mg. of cortisone over a five-day period. Temperature, pulse, and respiration recordings followed the usual pattern for burns of this severity (Fig. 1). The initial marked depression in the eosinophil count (Fig. 3) was consistent with the severity of the burn (Crassweller, Farmer, and Franks, 1950). With cortisone therapy the initial rise was followed by a return to low levels.

TEMPERATURE—

PULSE—PER MINUTE

FIG. 1.

Because of the oliguria, protein restriction seemed indicated and whole-blood transfusion was withheld at this time. Under this treatment an anaemia developed rapidly. The fluid intake, while adequate, was not excessive, so that dilution was not the cause of the low haemoglobin levels. The peripheral-blood smear showed large numbers of microspherocytes, as has been described in severe burns by Brown (1946). The depressed haemoglobin levels may thus have been secondary to haemolysis. Following the return of renal function, 500 ml. of whole-blood transfused on the third day failed to restore the haemoglobin level. Fear of renal complications prevented further transfusion, although it is evident, in retrospect, that transfusions were probably indicated. The anticipated drop in total plasma protein levels did not occur (Fig. 4), and the non-protein nitrogen values remained within normal limits throughout. It is difficult to account for the low total-urinary-nitrogen excretion (Fig. 5) in the face of the usual burn response, coupled with adequate fluid intake and cortisone therapy. As reviewed by Crassweller, Farmer, and Franks (1950), all of these might be expected to result in increased nitrogen excretion. Early hyperglycaemia did not occur, but rising non-fasting blood-sugar levels (Fig. 5), unaccompanied by ketonuria, and in the presence of a relatively constant glucose intake, are perhaps associated with the cortisone therapy. A rising 17-ketosteroid excretion level also suggests a cortisone effect. At necropsy the normal quantity and distribution of sudanophilic material

TOTAL FLUID INTAKE—

TOTAL FLUID OUTPUT—

FIG. 2.

CORTISONE—MILLIGRAMS

EOSINOPHILS—PER CU.MM.

FIG. 3.

found histologically in the adrenal cortices probably indicates that death was not secondary to adrenal exhaustion (Sayers and Sayers, 1949; Cain and Harrison, 1950).

The second case received cortisone 100 mg. daily, beginning on the third day (Fig. 3), following which she improved, and her clinical course was most encouraging. The temperature dropped almost immediately. She was bright and cheerful and displayed a keen appetite. Cortisone was stopped on the eighth day after a total dose of 600 mg. had been given.

After the first change of dressings on the tenth day there followed a slow progressive clinical deterioration. The appetite vanished and it became necessary to feed through a stomach-tube. The temperature

HEMOGLOBIN- GRAMS PERCENT (P.E.) **PLASMA PROTEINS- GRAMS PERCENT**

FIG. 4.

assumed a typical septic course and this was reflected in the pulse (Fig. 1) and respirations. A retrograde urinary infection was feared and the catheter was removed. The white blood count reached a level of 32,500 per c.mm. on the eleventh day. Repeated blood cultures were sterile.

During the period of cortisone therapy the eosinophils increased somewhat over the initial depression secondary to the burn (Fig. 3) but remained below the lower limit of normal, suggesting to us at the time that adequate cortisone was being used. However, a steady drop in the daily excretion of 17-ketosteroids in the urine from the third to the tenth day would suggest, from this criterion (Sprague *et al.*, 1950), that the total cortisone dosage was inadequate. A further drop from the eighth to the twelfth day suggests that the production of endogenous corticoids was depressed and remained so during this period. Unfortunately, owing to withdrawal of the catheter, 17-ketosteroid determinations were not available after the tenth day. (Because of the involved nature of the urinary 17-ketosteroid determination (McGill University Clinic modification of the Zimmermann reaction—Hawk *et al.*, 1947), the results were not available to us on a day-to-day basis. Eosinophil counts were therefore followed as the immediate criterion of cortisone therapy (Sayers, 1950). We are now attempting to apply the skin test described by Shuman and Finestone (1950) as a rough measure of corticoids in the circulation.) Continued depression of the eosinophil counts between the eleventh and fifteenth days

suggested that the patient was able to respond to the increased stress associated with the onset of infection. Eosinophil counts from the twentieth day onwards led us to believe that the patient was producing adequate corticoids. However, despite the trend of the eosinophil count, post-mortem sections of the adrenal cortices showed a marked decrease in sudanophilic material in the fasciculated and reticularis, and to a smaller extent in the glomerulosa. This suggests adrenal exhaustion (Sayers and Sayers, 1949; Cain and Harrison, 1950) and possibly indicates that 17-ketosteroid excretion estimations are a more reliable guide to adrenal function than the eosinophil count.

The question arises whether or not the administration of cortisone bore any relation to the development of the subsequent infection in the burn. With this in mind, a fractionation of the plasma proteins from a post-mortem sample of heart blood was carried out through the kindness of Dr. A. G. Gournall, Department of Pathological Chemistry, University of Toronto. Using solutions of sodium sulphate of varying percentage as precipitant, the total plasma protein was found to be 4.85 g. per 100 ml. With a 26% solution of sodium sulphate the yield was 2.55 g. of globulin and 2.30 g. of albumin per 100 ml. Using 15% sodium sulphate, the total globulin fraction amounted to only 0.25 g. per 100 ml. Further work is required to determine the significance of this apparently low value. The clinical course in this case, however, was fairly typical of

BLOOD SUGAR- MILLIGRAMS PERCENT **TOTAL URINARY NITROGEN- GRAMS PER DAY**

FIG. 5.

Ps. pyocyanea infection as reviewed by Stanley (1947).

According to the tables of mortality probabilities in burns, Case 3 had less than a 5% chance of survival under modern burn therapy. He responded well from the start, even before the administration of cortisone. He did not develop any evidence of pulmonary oedema, despite the fact that on the second day he received 15,500 ml. of fluid (Fig. 2). He did, however, develop marked peripheral oedema, making it necessary by the third day to split the body cast. This oedema probably accounts for the marked positive fluid-balance at this time. Cortisone therapy was begun on the fourth day and continued to the twenty-seventh day. Eosinophil counts were found to be depressed on the tenth, twelfth, and twenty-fourth days (Fig. 3). The cortisone dosage was tapered off on the nineteenth and finally stopped on the twenty-seventh day. The very high counts on the following days may indicate that the endogenous production of corticoids was somewhat depressed. The patient experienced a remarkable state of well-being, almost euphoria, during the period of cortisone administration and after its cessation. Also, he managed a sizeable calorie intake, averaging over 4,000 calories daily and on three occasions reaching 7,000 calories. Although it has been reported (Ragan *et al.*, 1950) that too much cortisone may delay wound-healing, no such difficulty was encountered in this case, despite the fact that the first graft was made during the period of cortisone administration.

Summary

Three cases of severe burn are presented in which routine burn therapy was supplemented by the administration of cortisone acetate.

The first patient, who suffered a 55% burn, died despite cortisone therapy. He had a normal histological distribution of lipid material in the adrenal cortices at necropsy.

The second patient, who suffered a 30% burn, received cortisone from the third to eighth days, during which period she was remarkably well. Her condition deteriorated clinically after the initial change of burn dressings on the tenth day. She died on the twenty-fourth day, death apparently being due to sepsis. The finding of markedly decreased sudanophilic material in her adrenal cortices suggests adrenal exhaustion at the time of death.

The third patient, who suffered a 70% burn, has done well. He received cortisone from the fourth to twenty-seventh days and displayed a remarkable state of well-being and a keen appetite. This unusual recovery may be related to the cortisone therapy.

We wish to acknowledge the assistance of M. D. Maxmen and A. G. Stocks in the preparation of this paper.

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AN UNUSUAL COMPLICATION OF MYANESIN THERAPY IN THE TREATMENT OF TETANUS

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"Myanesin" (α - β -dihydroxy- γ -(2-methylphenoxy)-propane; mephenesin) was introduced into clinical use by Berger and Bradley (1947), and was first used for relief of spasm in two cases of tetanus by Belfrage (1947), with encouraging results. Torrens, Edwards, and Wood (1948) treated a moderately severe case of tetanus with a combination of intramuscular and intravenous injections of myanesin, giving 22 g. in nine days, with considerable benefit to the patient. Davison, Ward, and Pask (1949) also treated two cases. The first case, after a period of treatment with curare and sedatives, was given intermittent intravenous injections of myanesin and recovered. The second was more seriously affected, and myanesin was used from the beginning of treatment. When it was found that a single intravenous injection controlled the spasms for only about 30 minutes, an intravenous glucose-saline drip was set up and myanesin added in varying amounts according to the condition of the patient. After 26½ hours of continuous myanesin treatment haemoglobinuria was observed and the myanesin was discontinued, but the patient immediately relapsed and died from violent spasms two hours later. Macdonald (1949) combined intravenous myanesin with intravenous thiopentone, giving 1–1.5 g. myanesin and 0.5–0.75 g. thiopentone in each 600 ml. of glucose-saline. In 23 days he gave a total of 40 g. myanesin and 32.75 g. sodium thiopentone. No haemoglobinuria occurred, and the patient, a child aged 8, recovered. Godman and Adriani (1949) used the American oral preparation "tolserol" in eight cases of tetanus; all but one of their cases were mild. They found that in doses ranging from 62.5 to 750 mg. in children, and up to 3,500 mg. in adults, it was an extremely satisfactory relaxing agent.

Case Reports

The following are reports of two cases of tetanus in which oral myanesin was used. Rectal thiopentone was also given in the first case.

Case 1.—A man aged 38, an inmate of a colony for mental defectives but of fairly high mental grade, was employed as an agricultural labourer. He gave no history of recent injury. On March 12, 1950, he complained of a painful stiff neck, which was thought to be due to fibrositis; he remained in bed but had no special treatment. The pain increased in severity and spread from the neck to the trunk and legs, and on the morning of March 16 he had a generalized convulsion. He was admitted to hospital, under the care of M. L. N. and J. D. R., at 2.30 p.m. on that day. On examination he was seen to be a well-built muscular man; there was no external injury, and he was fully conscious, flushed, and sweating profusely. There was rigidity of the neck and shoulder muscles with trismus and risus sardonicus. The erector spinae, the anterior abdominal muscles, and all muscles of the legs were in persistent spasm, and clonic contractions of the legs occurred on attempts to flex the knees. The arms were unaffected. No abnormalities were found in the heart, lungs, or central nervous system.