Conclusions

Anticoagulant therapy, suitably controlled by specialized techniques, reduces by one-half the mortality rate during the first six weeks after myocardial infarction. Our experience is that it appears to benefit males to a greater extent than females, particularly men whose myocardial efficiency was only slightly impaired before the acute damage was sustained.

Thrombo-embolic complications are reduced by half, and, when they do occur, fatalities are lessened.

Anticoagulant therapy cannot succeed in the absence of strict attention to the established methods of treatment. It does not shorten the stay in bed.

It should be considered for every sufferer from myocardial infarction. This implies an extension of laboratory facilities for the regulation of treatment and a greater number of hospital beds set aside for this purpose. A scheme for domiciliary laboratory control is desirable if the practitioner is to continue to care for these patients.

For the purposes of this investigation Professor Stanley Davidson, Dr. W. D. D. Small, and Dr. W. A. Alexander have kindly given us access to patients suffering from coronary thrombosis under their immediate charge in the Royal Infirmary. We are also indebted to Mr. George Waugh, F.F.A., of the Scottish Statistical Research Bureau, for help in the statistical analysis of our findings.

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CAPILLARY RESISTANCE AND ADRENOCORTICAL ACTIVITY

BY

H. N. ROBSON, M.B., M.R.C.P.Ed.

AND

J. J. R. DUTHIE, M.B., F.R.C.P.Ed.

(From the Department of Medicine, University of Edinburgh; Rheumatic Unit, Northern General Hospital; and the Eastern General Hospital, Edinburgh)

The starting-point of the present investigation was the observation that the resistance of skin capillaries to rupture by negative pressure rises sharply after many types of surgical operation (Scarborough, 1944). It was decided to study the effects on capillary resistance of other types of tissue damage. The variety of such types of damage which produced increased capillary resistance led to the possibility that this rise might be produced by any form of non-specific stress. Positive results were obtained after the application of various forms of stress. Interest was then stimulated by recent work on the physiology of the pituitary – adrenal axis, and it seemed possible that all the conditions which had been investigated were such as would lead to activation of this axis through the release of endogenous adrenaline or through some other pathway as yet unknown. This paper describes the investigations outlined above, leading to the study of the effects of the injection of adrenocorticotrophic hormone (A.C.T.H.) on capillary resistance.

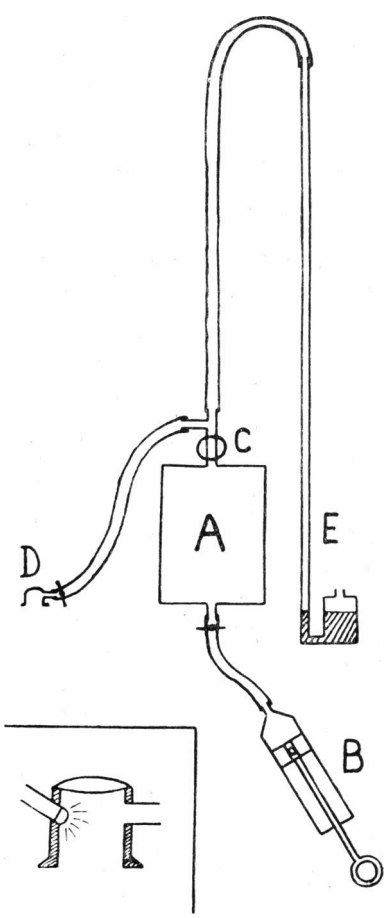

FIG. 1.—Diagram of apparatus used.

Methods

Capillary resistance has been measured throughout these studies by a negative pressure method. The apparatus (Fig. 1) was the same as that used by

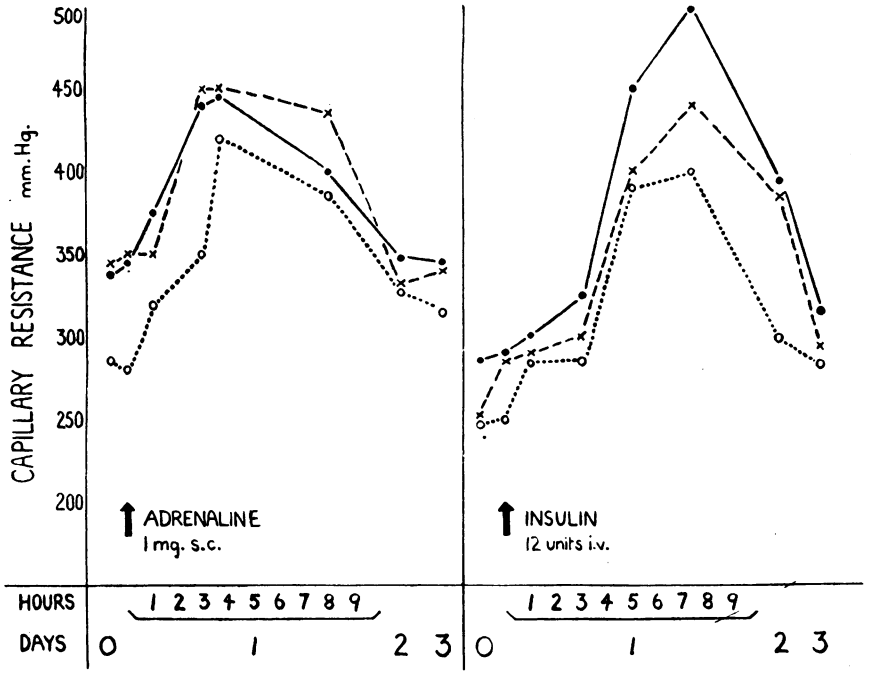

FIG. 2.—Changes in capillary resistance following (*a*) the injection of adrenaline, and (*b*) the production of insulin hypoglycaemia.
×----× Medial elbow region. O.....O Lateral elbow region.
●——● Wrist region.

Scarborough (1941). Negative pressure is created in the reservoir (A) by means of a suction pump (B). The control valve (C) allows suction to be applied to the skin in the test area through the cup (D). The degree of negative pressure is recorded on the mercury manometer (E). The suction cup used has an internal diameter of 20 mm. A lens of ×10 is incorporated in the roof of the cup. Standard illumination is obtained from an endoscope bulb which projects from the wall of the cup and is lit by a 2-volt dry battery.

The principle employed in using this apparatus was the determination of the "critical petechial pressure"—that is, that negative pressure which when applied for 30 seconds would produce one or two petechiae only in the test area. At each estimation three standard areas on the volar aspect of the forearm were tested (Scarborough, 1941), the same arm being used throughout studies on any one patient, and, when recorded daily, readings were taken at approximately the same hour. In order to reduce the number of trial readings at any one estimation, alterations in pressure were usually made at intervals of 500 mm. Hg. It has been found by experience that when any given pressure produces up to but not more than 10 petechiae it is usually unnecessary to make further trial, since a pressure of 50 mm. less will not produce any petechiae. If more than 10 petechiae are produced, then it is necessary to repeat the observation at a lower pressure in an immediately adjacent area. For the purposes of graphing results only, it has been assumed that between the intervals of 50 mm. of pressure the "critical petechial pressure" is proportional to the number of petechiae produced.

With the technique described here, the average range of normal capillary resistance is 250 to 350 mm. Hg, but occasional wide variation in normal individuals is encountered within a range of 200 to 450 mm. Hg (Bell, Lazarus, Munro, and Scarborough, 1942).

Factors Influencing Capillary Resistance

Physical Agents—Heat, Cold, and Ultra-violet Light.—The environmental temperature is known to affect capillary resistance. Von Borbély (1930) showed that immersion of the body in a warm bath caused a fall in resistance, while a cold bath gave rise to increased resistance. Rossman (1940–1) showed that heating of the whole body in an inductotherm caused lowering of resistance during the period of heating, followed by a rapid rise to supranormal levels when heating was discontinued Patients undergoing inductotherm treatment have been studied here. No observations were possible during the period of heating,

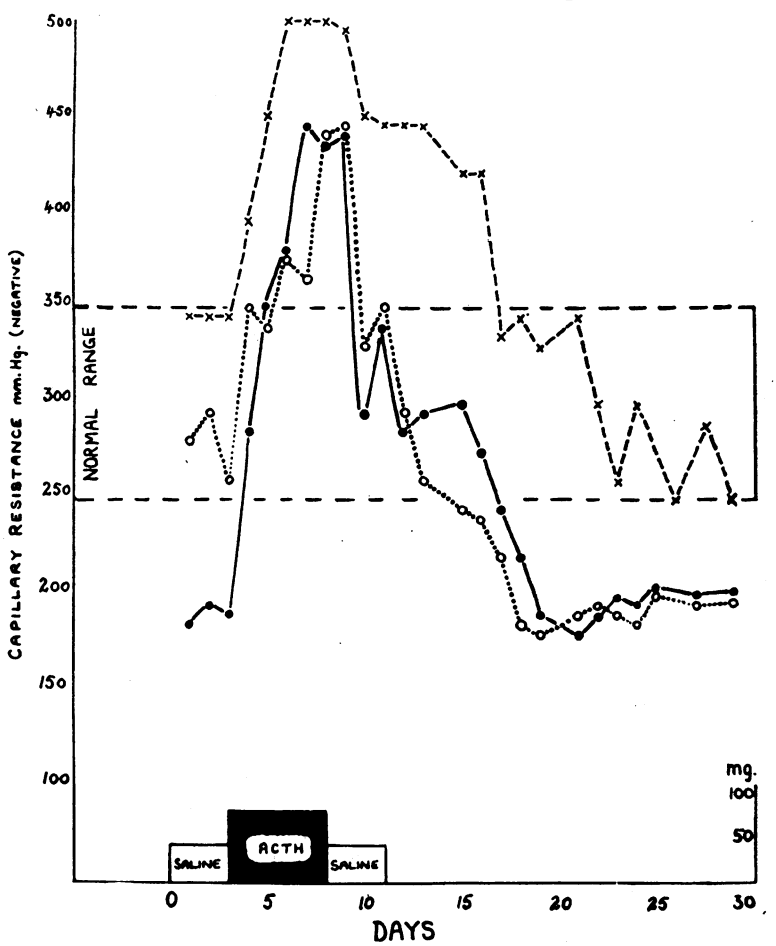

FIG. 3.—Changes in capillary resistance following the administration of 75 mg. A.C.T.H. daily for five days in a case of rheumatoid arthritis.

Table Showing Results in Cases of Rheumatoid Arthritis

Case No.	Area	Range of Readings in Control Period		Readings at 4 hr. after 25 mg. A.C.T.H.		Readings at 8 hr. after 25 mg. A.C.T.H.		Maximum Resistance Attained (mm.Hg)	Time to Reach Maximum (hr.)	Time Taken to return to Control Levels (days)	Total Dose of A.C.T.H. (mg.)
		Capillary Resistance (mm.Hg)	Eosins. (c.mm.)	Capillary Resistance (mm.Hg)	Eosins. (c.mm.)	Capillary Resistance (mm.Hg)	Eosins. (c.mm.)				
1	M.E. L.E. W.	240–275 100–250 190–290	141–225	—	52	—	—	400 350 500	72	10	1,050
2	M.E. L.E. W.	325–350 200–250 225–250	166–255	400 250 350	92	360 240 300	114	500 390 400	26	2	75
3	M.E. L.E. W.	340–350 260–300 190–200	152–184	400 375 300	88	350 290 250	109	500 450 450	84	10	375
4	M.E. L.E. W.	320–350 250–300 200–300	66–145	400 400 270	26	450 400 270	50	500 500 420	72	14 (2 areas only)	375
5	M.E. L.E. W.	250–290 200–230 275–290	330–386	300 220 300	120	350 275 380	—	400 350 500	72	12	375
6	M.E. L.E. W.	300–340 250–340 300–340	602–881	380 370 450	266	370 360 400		500 470 500	72	40	375

M.E., medial elbow region. L.E., lateral elbow region. W., wrist region.

but readings taken after removal of the patient from the inductotherm confirmed Rossman's observation that a marked increase in resistance occurs. Franke (1943) reported that exposure to ultra-violet light gave rise to diminished resistance during the period of skin erythema, but that if exposure was continued resistance rose to supranormal levels.

X-ray Irradiation.—Capillary resistance has been measured in patients having radiotherapy for various types of malignant disease. In most cases a marked rise in capillary resistance occurred within three to four days of the beginning of therapy and was maintained during the course. These findings are to be fully described elsewhere (Robson and Court Brown, to be published).

Mitotic Poisons: Nitrogen Mustard.—The intravenous injection of nitrogen mustard in cases of reticulosis has also been found to cause a sharp rise in capillary resistance, sustained for some days after completion of the course of injections.

It seemed possible that, since the agents described above caused some degree of tissue damage, their effects on capillary resistance might be due to the action of histamine or histamine-like substances released by tissue breakdown.

Histamine.—Franke (1943) reported that 1 mg. of histamine injected subcutaneously caused an initial fall in capillary resistance, which was maximal in about 20 minutes, with a return to basic readings in about 45 minutes. He did not record observations beyond that point. Wyss and Gianoli (1946) confirmed these findings. The technique employed in the present investigation was the intravenous infusion of 3 mg. of histamine in a saline drip over a period of one to two hours, usually in cases of rheumatoid arthritis. Capillary resistance was found to fall during the period of infusion of the drug, returning to basic levels in about two hours, and rising thereafter to supranormal levels, the increase being sustained for about 24 hours. The pattern of change in capillary resistance following the infusion of histamine, while bearing some resemblance to the effects of heating and burning, was not the same as that produced by cold, or by surgical operations, irradiation, or mitotic poisons.

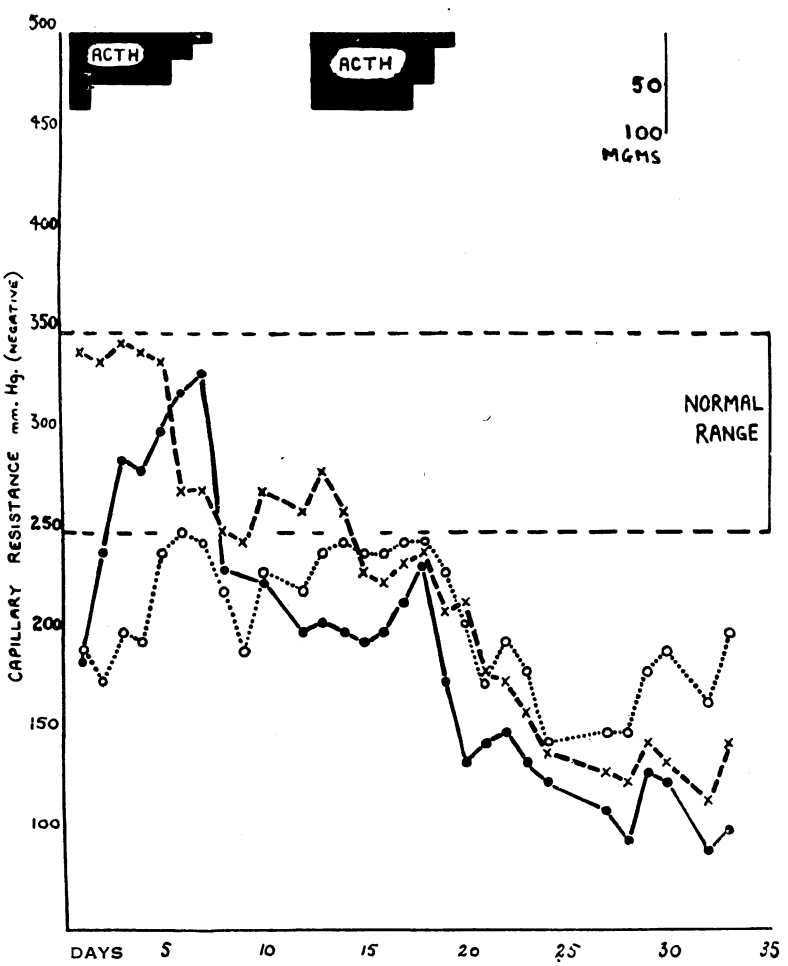

FIG. 4.—Changes in capillary resistance in the case of lupus erythematosus which showed a poor clinical response to A.C.T.H., and in which there was a fatal termination.

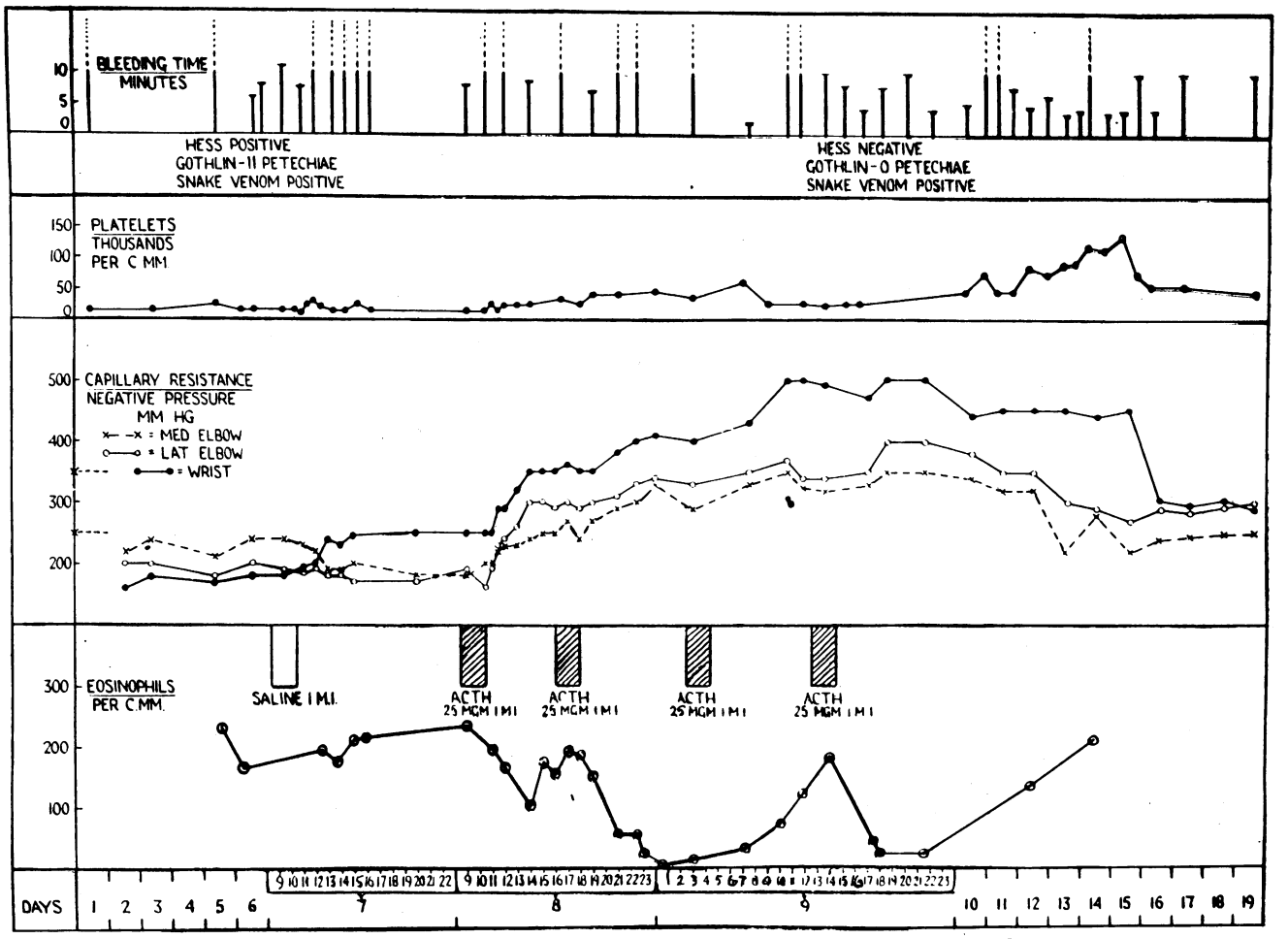

FIG. 5.—Results of the administration of A.C.T.H. in Case A (thrombocytopenic purpura)—first course.

Protein Shock by T.A.B. Vaccine.—Protein shock produced by the injection of T.A.B. vaccine was studied. A fall in resistance was generally recorded during the period of mounting pyrexia, but this was followed by a rapid rise to supranormal levels, reaching a maximum in three to four hours and thereafter slowly returning to the baseline in 36 to 48 hours.

Adrenaline.—It was decided to observe the effects of the injection of adrenaline, since the "alarm reaction" of Cannon is produced by the endogenous release of this substance. Observations were made following the injection of 1 mg. of adrenaline intravenously or 1 to 2 mg. subcutaneously. With either route a rise in capillary resistance has constantly been found, detectable within two hours of the injection, reaching a maximum in four to six hours, and thereafter returning to base levels in 24 to 36 hours. An example is shown in Fig. 2. Similar results have been described by Parrot, Lavollay, and Galmiche (1944) and by Lavollay (1944).

Insulin Hypoglycaemia.—The results obtained by the injection of adrenaline prompted the study of the effects of hypoglycaemia, since this is known to be an effective stimulus to the endogenous release of adrenaline. Observations were made following the injection of soluble insulin, either intravenously in doses of 10 to 15 units, or subcutaneously in doses of 30 to 50 units. One example of the result is shown in Fig. 2. An increase in capillary resistance is usually detectable about one to two hours after the hypoglycaemia is manifest, reaching a maximum in four to six hours, and returning to control levels in about 48 hours.

The observations, when considered in the light of recent work which suggests that adrenaline stimulates the production of A.C.T.H. from the anterior pituitary, led to the idea that increased capillary resistance might be a manifestation of increased adrenocortical activity.

A.C.T.H. and Capillary Resistance

In the course of wider clinical investigations an opportunity arose to study the effects of A.C.T.H. on capillary resistance. Among the cases which have been studied were six examples of rheumatoid arthritis, two of ankylosing spondylitis, two of disseminated lupus erythematosus, and two of idiopathic thrombocytopenic purpura.

Rheumatoid Arthritis

Six patients suffering from this condition have been studied. Fig. 3 illustrates the changes in capillary resistance resulting from the administration of 75 mg. A.C.T.H. daily for five days in one of these cases. The accompanying Table gives brief details of the findings in the six cases. Illustrated are the changes in response to the first dose (25 mg.), the time taken to reach maximum resistance on a dosage of 25 mg. eight-hourly, and the time taken for capillary resistance to return to control levels after the course was completed. It may be seen that a single dose of 25 mg. of A.C.T.H. produced a significant rise in one or more areas within four hours in all except one case, in

which the response was delayed. In this latter case resistance was raised at eight hours after the injection, by which time the others had in general shown a tendency to return to base levels. In all cases, continued administration of A.C.T.H. in doses of 25 mg. eight-hourly resulted in a marked elevation of capillary resistance, reaching a maximum in about 72 hours. Resistance was maintained at this high level for the remainder of the period of administration. When A.C.T.H. was stopped the resistance fell at varying speeds, reaching base levels again in 10 to 14 days. (In Cases 4 and 6 the return was much slower.) No case has been encountered in which a significant fall in eosinophils has not been accompanied by a definite rise in capillary resistance. The extent and speed of the increase in resistance, however, have not necessarily corresponded exactly with the percentage fall in eosinophils. The extent and duration of the increased resistance have borne only a rough correspondence to the clinical effects achieved by the A.C.T.H.

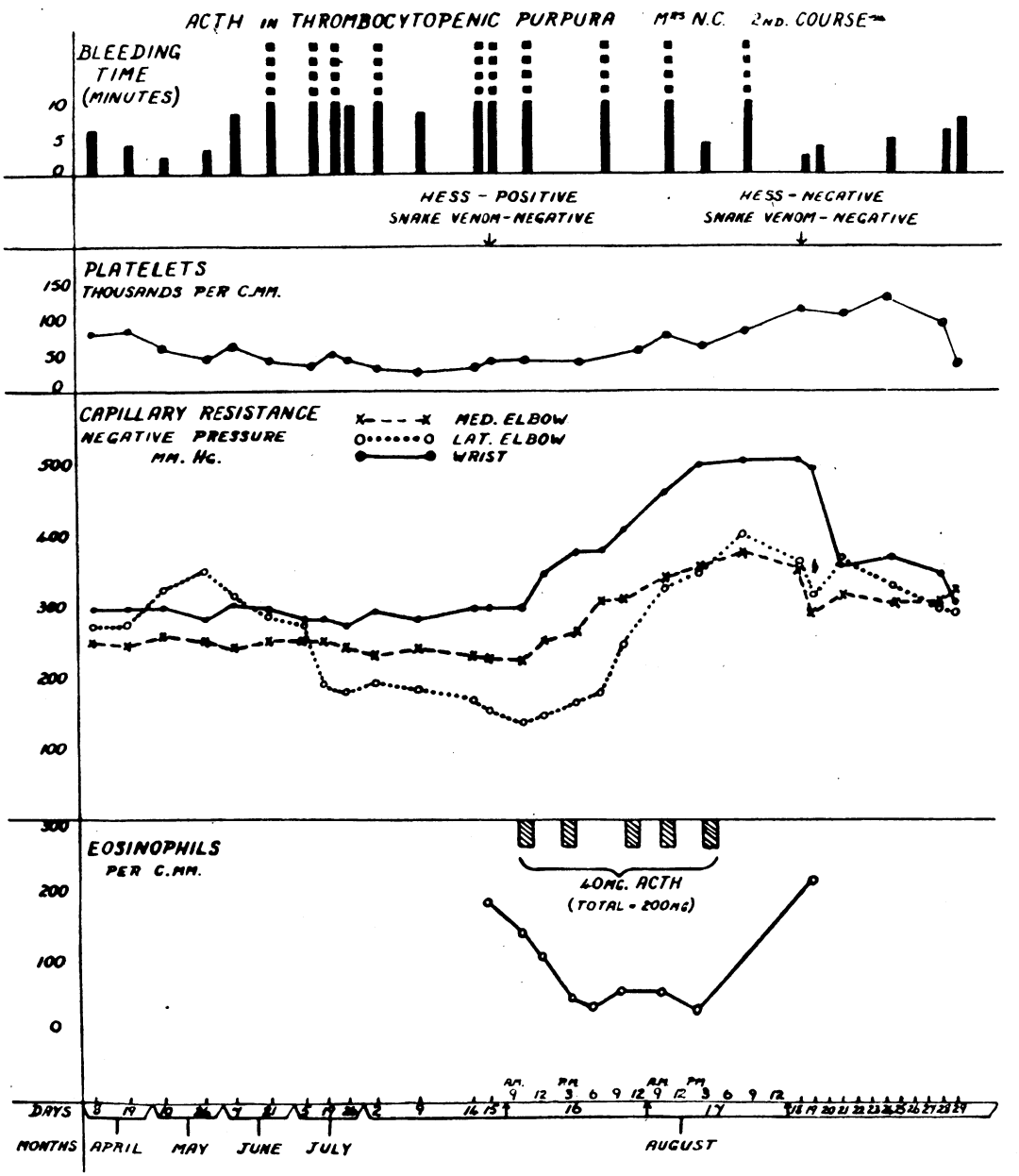

FIG. 6.—Results of the administration of A.C.T.H. in Case A—second course.

Spondylitis Ankylopoietica

Two patients suffering from this condition have been studied. In both a marked increase in capillary resistance was observed following the administration of 75 mg. daily. Resistance reached maximum level in both about 48 hours after the first injection. In both cases resistance fell quickly on completion of the five-day course of A.C.T.H.

Disseminated Lupus Erythematosus

Two patients suffering from this condition have been studied. In both cases capillary resistance was low in the observation period. In one case, eosinophils, which had been entirely absent from the peripheral blood, reappeared before A.C.T.H. was given. A course of A.C.T.H. lasting seven days (total dose 340 mg.) resulted in a marked clinical improvement, a reduction in circulating eosinophils, and a definite increase in capillary resistance. This increase was not long sustained after A.C.T.H. was discontinued, and resistance returned to base levels in four days. Clinical relapse was also quickly evident. The findings in the second case are illustrated in Fig. 4, where it may be seen that the expected increase in resistance did not take place. The patient showed a poor clinical response to A.C.T.H.; her condition steadily deteriorated and death occurred. Eosinophils were absent from the peripheral blood in this case throughout the entire period of observation, before, during, and after the administration of A.C.T.H. At necropsy both adrenals were found to be small, and on section it was noted that lipoid was extremely scanty in the zona fasciculata.

Idiopathic Thrombocytopenic Purpura

Since low capillary resistance is generally regarded as one of the principal features of idiopathic thrombocytopenic purpura, it seemed of interest to ascertain the effect of giving A.C.T.H. in this condition. Reports of two cases follow.

Case A.—A woman aged 33 had had a prolonged episode, starting in 1946 and continuing until spontaneous remission occurred in 1948. During this time she had suffered from ecchymoses and recurrent petechial rashes, but no haemorrhagic incidents had occurred. In December, 1949, on the twelfth day of the puerperium of a normal pregnancy and delivery, ecchymoses and petechiae reappeared. These, together with thrombocytopenia, continued without remission up to the time of the present investigation. The results of the initial administration of 100 mg. of A.C.T.H. in four divided doses are shown in Fig. 5. It may be seen that a definite rise in capillary resistance occurred, reaching a maximum after 75 mg. had been given. When the drug was discontinued, capillary resistance returned slowly towards the control levels in approximately seven days. During the period of elevated resistance the Hess test became negative, but the snake-venom test remained positive; no significant change occurred in platelet counts and the bleeding-time was little altered. It must be noted, however, that a moderate increase in platelets was recorded (maximum about the seventh day) after A.C.T.H. had been given, and that a tendency towards reduction in bleeding-time had become apparent about this period. Clinically, a definite remission resulted, and this persisted for three months, though platelet counts and capillary resistance had returned to low levels. Ecchymoses and petechiae then reappeared and the clinical condition rapidly reverted to that found before the first course of A.C.T.H. As shown in Fig. 6 a second course of A.C.T.H., totalling 200 mg., was given in 40-mg. doses over a period of 48 hours. This resulted in changes similar to those observed previously in capillary resistance, bleeding-time (more definitely reduced on this occasion), and platelets (again a delayed slight increase). Clinical remission has again been produced, although at the time of writing this had been followed for only three weeks. It must be noted that, although the amount of A.C.T.H. given was doubled in the second course, the effects produced were no greater than, if indeed as great as, in the first course.

Case B.—A man aged 32 presented with a history of bruising and petechial haemorrhages for three months, and of bleeding from the gums for one week. The clinical and haematological findings conformed to the diagnosis, and during observation over a period of three weeks there was no sign of remission. As shown in Fig. 7, A.C.T.H. was given in doses of 40 mg. eight-hourly to a total of 340 mg. This resulted in a marked increase in capillary resistance, a definite reduction in bleeding-time, conversion of both the positive-pressure and the snake-venom tests to negative, and a moderate thrombocytosis which was maximal about nine days later. Bleeding from the gums stopped on the second day of A.C.T.H. administration, no further bruises or petechiae appeared, and the patient has remained in complete clinical remission for five weeks. In contrast to Case A, capillary resistance and platelets have remained above the pre-A.C.T.H. levels and the bleeding-time has been maintained within the normal range.

Discussion

The negative-pressure method of estimating capillary resistance has not been so widely employed as have positive-pressure methods such as the Hess, Rumpel-Leede, or Göthlin tests. First suggested by Hecht in 1907, the suction method has been used by such authors as da Silva-Mello (1929, 1930), Mengler (1930), Von Borbély (1930), Adant (1936, 1938), Franke (1943), and Parrot, Lavollay, and Galmiche (1944) on the Continent; by Dalldorf (1933), Dalldorf and Russell (1935), Cutter and Johnson (1935), and Elliott (1938) in America; and by Scarborough (1941, 1943, 1944) and Robson (1949) in this country. The merits and demerits of the method are reviewed by Munro, Lazarus, and Bell (1947).

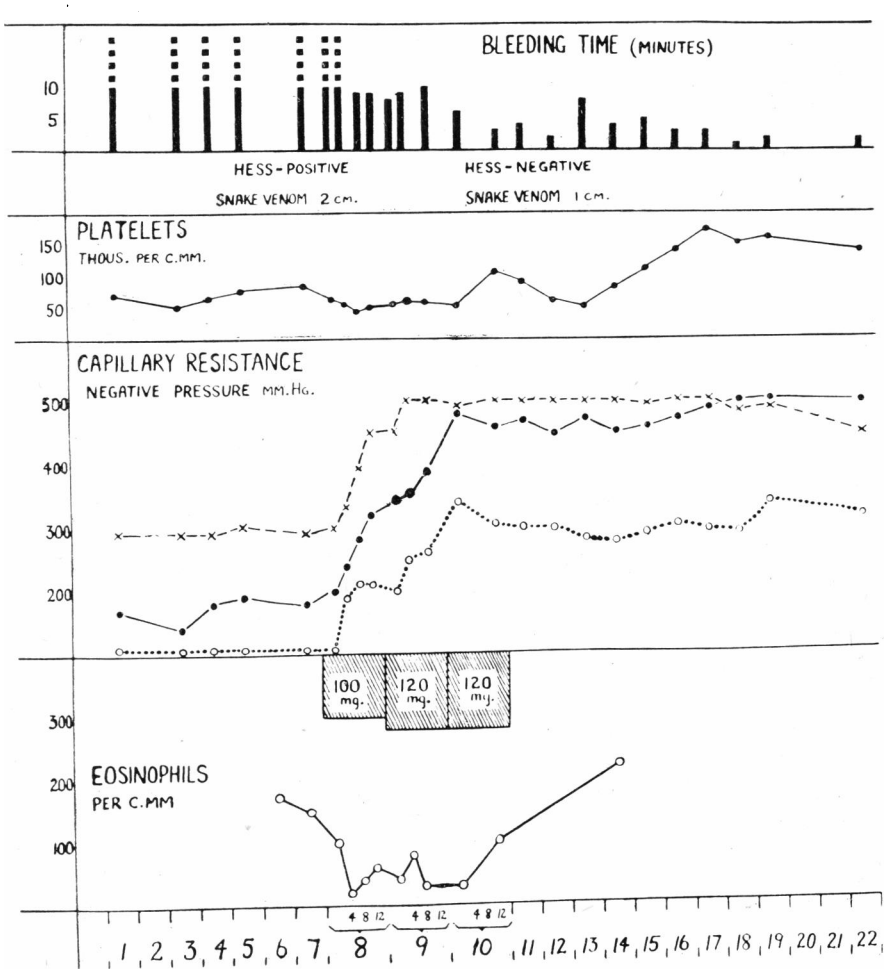

FIG. 7.—Results of the administration of A.C.T.H. in Case B (idiopathic thrombocytopenic purpura).

In the present study, the use of the negative-pressure method has permitted the detection of an increase in capillary resistance, often to markedly supranormal levels, occurring as a result of several different stimuli. These preliminary observations suggest strongly that this rise in resistance is mediated by adrenocortical activity. The number of cases treated with A.C.T.H. is not great, but it seems probable that the extent and duration of the increase in resistance are roughly proportional to the degree of adrenocortical stimulation. In the cases of rheumatoid arthritis, however, the capillary changes did not necessarily reflect accurately the clinical response of the patients to A.C.T.H. In the sixth case of rheumatoid arthritis (see Table), a dramatic clinical remission was produced by A.C.T.H., but this was short-lived. The capillary resistance, however, which was raised to high levels, remained elevated for a considerable period, though complete clinical relapse had occurred. In the fifth case, on the other hand, a prolonged clinical remission was produced by A.C.T.H., but capillary resistance

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.

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THREE CASES OF SEVERE BURN TREATED WITH CORTISONE*

BY

P. O. CRASSWELLER, M.D.

A. W. FARMER, M.D.

W. R. FRANKS, M.D.

(From the Royal Canadian Air Force Institute of Aviation Medicine and the Department of Surgery, Hospital for Sick Children, Toronto)

AND

A. D. McLACHLIN, M.D.

Professor of Surgery, University of Western Ontario, London, Canada

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

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