Acute Circulatory Collapse of the Adrenalectomized Dog Following Plasma Infusion

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Adrenalectomized dogs maintained on desoxycorticosterone acetate developed a fatal circulatory collapse when given normal dog plasma. They showed general restlessness, a rapid fall in blood pressure and cardiac index, a decline in central venous pressure and general prostration. Most dogs developed a bloody diarrhea and a minority showed edematous swelling of the face with itching. Animals with intact spleens exhibited marked hemoconcentration, splenectomized animals did not. Blood and plasma specific gravity determinations offered no evidence for gross plasma loss. Diphenhydramine prevented the collapse.

For 25 years it has been commonly accepted that death in terminal adrenal insufficiency is the result of a "peripheral circulatory collapse." A current thesis is that this collapse is qualitatively the same as that involved in irreversible shock in the animal with intact glands. Two major facts prevent a complete acceptance of this thesis: Adrenal crisis may be precipitated by non-hemorrhagic procedures which, in themselves, probably produce no decline in blood volume, whereas shock in the intact dog can be experimentally produced only when there is some degree of blood volume reduction. Second, even in its earliest stages, the arterial pressure fall of adrenal crisis is not reversed by blood transfusions. In fact, when an infusion of aseptically collected dog plasma was given an adrenalectomized dog in early adrenal insufficiency, a fulminating circulatory collapse developed which led to death within a few hours. This collapse was accompanied by edema and marked hemoconcentration, which suggests a fault in capillary function.

We have repeated the plasma infusion experiments on adrenalectomized dogs being maintained on desoxycorticosterone acetate (DCA) which showed no signs whatsoever of impending adrenal insufficiency—the sudden circulatory failure appeared nonetheless. Our results, however, do not lend themselves to a simple interpretation of capillary failure per se.

METHODS

A total of 34 adult, male dogs, 8 to 14 Kg. in weight, were adrenalectomized in a single stage operation, given 50 mg. cortisone acetate and 5 mg. DCA on the first postoperative day, and then 5 mg. cortisone and 2 mg. DCA/day until the wounds had healed. They were then placed on 2 nig. DCA/day for at least 14 days before they were used. All animals were eating well and maintaining their body weight when selected for the experiment. Five of this group were splenectomized at the time of the adrenalectomy.

Blood was removed from healthy normal dogs, except in one case where it was taken from an adrenalectomized dog being maintained on DCA. It was drawn aseptically from a femoral artery into 250 ml. sterile bottles containing 15 ml. of 4 per cent sodium citrate. Any bottle not filled, and thus having an unduly high concentration of citrate, was discarded. The blood was promptly centrifuged, and the plasma siphoned through sterile tubing into another sterile bottle. The plasma was stored over night in a refrigerator, and brought to body temperature just before the infusion. The injection was given at the rate of 4 ml./min., into a femoral or saphenous vein, until 120 ml. had been administered. For 2 animals, the donor blood was mixed with 40 mg./250 ml. of heparin instead of citrate. The reactions of the recipient animals were not distinguishable from those seen when the citrated plasma was used.

Seven of the adrenalectomized dogs were unanesthetized when infused. They were placed on their sides on an animal board only for the pe-
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period of the infusion itself. No cardiovascular measurements were made on these dogs; the other seven were subjected to a more complete study after the administration of 20 mg. morphine sulfate and no more than 15 mg./Kg. sodium pentobarbital. In these dogs, central aortic pressure pulses were recorded optically by a sound passed into the ascending aorta. Cardiac index and total peripheral resistance (TPR = mean aortic pressure in mm. Hg/cardiac index in ml./sec./M.1) were calculated from these pulses. It should be recognized that the pulse contour technic may not be trustworthy in adrenalectomized dogs when the mean aortic pressure declines to around 50 mm. Hg. The cardiac index and the derived resistance values reported are of value, then, only in an attempt to isolate a primary change taking place during or shortly after the infusion, which might lead to the pressure fall. Unfortunately, no other measure of cardiac output can be used in this fulminating circulatory collapse seen in the adrenalectomized dogs. The points on the figures derived from pulse forms which might be indicating a falsely high cardiac index are designated by broken lines (distortion pulses).

The central venous pressure was measured with a saline manometer attached to a catheter passed into the thorax via the right external jugular vein. The level of the apex beat was used as the zero standard. Blood and plasma (Gp) specific gravities were measured on femoral venous blood by the falling drop technic, and cell fractions (Hct) calculated from these gravities. Pressure records were taken and samples drawn 4 times during the infusion, and at 10 to 15 min. intervals thereafter.

The use of Gp and Hct to assess the possibility of massive leakage of ultrafiltrate or plasma through the capillaries requires an accounting of the volume and the Gp of the administered plasma. It was assumed that the red cells, in the splenectomized dogs, were not lost from the active circulation during the infusion, but quantitatively diluted. This assumption has proven to be reasonably valid in a study still in progress on the cell fraction changes in nonadrenalectomized dogs after small infusions of plasma or blood. On this basic assumption, a value for the initial plasma volume \( CPV \), can be derived:

\[
CPV = \frac{(1-Hct_i) Hct_i - I}{(Hct_i - Hct_f)}
\]

where \( Hct_i \) and \( Hct_f \) are the calculated cell fraction before and at the end of the infusion, and \( I \) is the volume of infused plasma. This calculation then allows a calculation of the Gp value to be expected after the animal's own plasma has been mixed with that administered:

\[
\text{Expected Gp} = \frac{PV_i Gp_i + I Gp_i^*}{PV_i + I}
\]

where \( Gp_i^* \) is the specific gravity of infused plasma.

RESULTS

Unanesthetized-Adrenalectomized Dogs. Two animals on DCA maintenance therapy were given 120 ml. of aseptically collected normal dog plasma. By the end of the infusion both were showing signs of impending circulatory collapse, i.e., a low arterial pressure as judged from femoral palpation and extreme weakness when the animals were placed on the floor. Both were prostrate within 30 min. after the infusion. One showed edema of the face and snout, the other did not. Both passed copious fluid stools containing considerable blood. The edematous dog died in 14 hours, the other in 3 hours.

The topographic pattern of the edema and the presence of cutaneous itching in the same region, was similar to that described for an anaphylactoid reaction, which suggested that the administered plasma could have released histamine. Two more dogs were pretreated with 5 mg./Kg. diphenhydramine hydrochloride (Benadryl) 20 or 45 min. before the infusion, depending upon the mode of administration (intravenous or intramuscular). Neither animal showed untoward signs after the infusion, the blood pressure was judged to remain normal, and both survived. A fifth dog was given plasma with no pretreatment. When the characteristic signs had become quite marked (restlessness, face edema, bloody stools, low arterial pressure) it was given diphenhydramine intravenously. Within 4 hours the edema had noticeably decreased, the blood pressure had risen, and it survived.

To confirm the earlier report that this reaction to plasma was correctable by adequate DCA therapy, a sixth animal was given 15 mg. DCA in oil (intramuscularly) 18 hours before the infusion. It developed restlessness and itching, but no edema, passed a stool shortly after the infusion (not bloody), but did not suffer a fall in pressure, and recovered.

These findings prompted two questions:
1. Despite the rarity of transfusion reactions in normal dogs, could these results indicate an extreme sensitivity of the adrenalectomized animal to a blood type incompatibility?

2. Had there been a change in the blood itself after adrenalectomy so that normal plasma would be toxic, or incompatible, but plasma from another adrenalectomized dog would not? Plasma was collected from an adrenalectomized dog being maintained on DCA. On cross-matching with the cells of a recipient adrenalectomized dog, this plasma produced no agglutination. When this plasma was given in the usual manner, the animal was prostrate at the end of the infusion, the femoral pulse could not be palpated, and death followed 15 min. later. There was no edema.

**Hemodynamic Changes After Plasma Infusion in Anesthetized Dogs**

Splenectomized, Nonadrenalectomized Dogs. We have given either plasma or whole blood infusions to 10 splenectomized, nonadrenalectomized animals. In no case has a reaction similar to that seen in the adrenalectomized animals been observed. Hemodynamic changes during and after a 120 ml. plasma infusion in a representative animal are given in figure 1. Early in the infusion both systolic and diastolic pressures rose above control levels and the increases were maintained. The initial increase is largely referable to a rise in peripheral resistance, the later elevation to an increased cardiac index which accompanied cardiovacceleration. The central venous pressure remained steady.

**Fig. 1** Left. Hemodynamic and blood changes in the plasma injected splenectomized dog. A.P., aortic pressure; H.R., heart rate; C.I., cardiac index; T.P.R., total peripheral resistance; C.V.P., central venous pressure; G.p, plasma specific gravity (broken line, calculated expected Gp); Hct, calculated cell fraction.

**Fig. 2** Right. Hemodynamic and blood changes in the plasma infused adrenalectomized dog. A.P., aortic pressure; H.R., heart rate; C.I., cardiac index (broken line, values derived from distortion pulses); T.P.R., total peripheral resistance (broken line, values derived from distortion pulses); C.V.P., central venous pressure; G.p, plasma specific gravity (broken line, calculated expected Gp); Hct, calculated cell fraction.
There was a slight fall in Gp during the course of the infusion, but the level reached was not significantly lower than that to be expected by dilution with an infusion plasma of lower specific gravity (fig. 1, broken line). About 30 min. after the end of the infusion the Gp was again elevated to pre-infusion levels, indicating a continuous outward filtration of fluid; however, the cell fraction did not increase from the level reached at the end of the infusion in this period during which the Gp was rising.

**Adrenalectomized Dogs.** During the infusions, the adrenalectomized dogs exhibited some differences in hemodynamic picture. Figure 2 shows the data obtained from 1 of 2 dogs having intact spleens. As with the normals, both systolic and diastolic pressures were elevated early in the infusion. By the end of the infusion, the pressure had returned to the control level in one, was still elevated in the other. Unlike the normal dogs, the cardiac index remained fairly constant in both dogs, so that the arterial pressure rise was due to an increase in total peripheral resistance. The heart rate remained essentially constant.

Following the infusion there was a steady
fall in both arterial pressure and cardiac index. As the pressure fell the heart rate increased markedly. The central venous pressure continued to fall, and remained low until death.

Unlike the nonadrenalectomized dogs, the Gp remained near the expected value during the postinfusion period, giving no evidence for either loss or gain of ultrafiltrate. In contrast, the cell fraction rose sharply at the end of the infusion. In one dog this rise came at the same time as the pressure fall; in the other it preceded it by about 15 min.

Adrenalectomized-Splenectomized Dogs. The rise in cell fraction reported must have been due to splenic contraction, since it was not seen in 3 adrenalectomized-splenectomized animals (fig. 3). In all 3 dogs, the hemodynamic changes were similar to those reported above for nonspleenectomized dogs, but the arterial pressure began its steady decline earlier, during the period of the infusion. In the case presented, the Gp was clearly increased over that expected. The second dog showed only a minor and inconsistent rise in Gp, and the third a small fall. During the infusion, but perhaps not later, the increase in cell fraction of the first dog could be accounted for by a loss in ultrafiltrate as indicated by the elevated Gp. The other 2 dogs showed a decreased cell fraction after infusion, as expected.

Adrenalectomized-Splenectomized Dogs Treated with Diphenhydramine. Two adrenalectomized-splenectomized dogs maintained on DCA were given this antihistaminic drug, intravenously, 15 min. before the plasma infusion (fig. 4). They maintained the usual increase in aortic pressure values for some 45 min., and then showed a return to the preinfusion level. There was an elevation in heart rate and in cardiac index, continuing to the end of the experiment. Unlike the intact or the untreated adrenalectomized dog, these animals showed a decline in total peripheral resistance. The pressure rise was therefore entirely due to an increased cardiac index. The central venous pressure fell during the infusion, but began to rise toward the control values near the end of the experiment. The Gp fell to a level lower than expected from dilution by the infused plasma alone, and remained low. Despite this, the cell fraction returned toward the control levels after the infusion. Both animals appeared in good condition when the experiment was terminated.

DISCUSSION

There would appear to be some points of similarity between the response of the adrenalectomized dog to injected plasma and that of the adrenalectomized rat to injected dextran. In neither case is prior sensitization of the animal to the lethal agent required, yet the pattern of response is anaphylactoid in character. Dextran, in the rat, liberates histamine. Death can be prevented by prior administration of the antihistaminic drug Phenergan, by cortisone, and to a lesser extent by epinephrine. Any of these therapies prevent the development of cyanosis and prostration, but do not prevent a generalized edema. Therefore, death cannot clearly be attributed to a reduction in blood volume, per se.

That aseptically collected dog plasma should act as a histamine releaser is a strange postulate, yet we have not been able to indict any contaminant of this plasma as the lethal agent. The same fatal response was seen with heparinized plasma as with that containing citrate. No difference was seen whether the plasma contained traces of hemoglobin or was clear. Matching the plasma with the cells of the recipient gave no in vitro evidence of agglutination. Samples taken from the recipient after the infusion did not show evidence of an in vivo hemolysis. When present, the sharply localized edema indicated an anaphylactoid response. Such edema was seen in only half our unanesthetized adrenalectomized dogs, and never in the anesthetized dogs. Why the light anesthesia used should have reduced the incidence of this edema, if it did, is unexplained. What does seem clear is that the fatal collapse was not necessarily related to an excessive plasma leakage through damaged capillaries. This conclusion is quite opposite to that reached by earlier workers.
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who found marked hemoconcentration. Such a cell fraction increase was seen in our dogs with spleens intact, but any change was quite small after the spleens were removed.

Minor discrepancies were seen between the changes in plasma specific gravity and in the calculated cell fraction. In the nonadrenalectomized dogs the cell fraction did not increase despite a rise in Gp, indicating a gain of plasma from a peripheral depot of about 4 per cent. Three of 5 adrenalectomized dogs, 2 given diphenhydramine and 1 untreated, showed the opposite, i.e., a progressive increase in cell fraction not accounted for by ultrafiltrate shifts. A loss in circulating plasma of about 4 per cent is perhaps indicated here. These changes are neither large nor consistent enough to be of diagnostic value in assessing the status of peripheral bed function. They offer no evidence for an appreciable loss of circulating blood volume. The changes in cell fraction are in contrast to the large increase (about 55 per cent) seen in animals with intact spleens.

It would therefore appear that splenic contraction was an integral part of this reaction to the transfusion, produced either reflexively as the arterial pressure fell, or directly by some excitatory agent present in the plasma. There is evidence that our plasma did contain a stimulatory agent. During the infusion, all animals characteristically produced a rise in aortic pressure and in total peripheral resistance. It should be emphasized again that the rate of infusion was slow, and there was no measurable change in central venous pressure preceding or coincident with this rise. In a few animals, there was a cardioacceleration unheralded by a pressure fall. It is possible that the agent involved could be serotonin, released from the formed elements of the donor's blood during the preparation of the plasma.

No depressor action of plasma was seen in the animals with intact adrenal glands. This does not rule out the possibility that the plasma may have produced some change, such as release of histamine, which was of negligible importance in the normal dog, but was lethal in the highly sensitive, adrenalectomized dog. There is some similarity in the hemodynamic pattern seen during collapse of the infused adrenalectomized dog and that seen in a normal dog given an intravenous infusion of 15 mg./Kg./min. of histamine base. In both the cardiac index is reduced, the central venous pressure falls and the heart size becomes small. In both there are cardiac rhythm changes, more marked in the adrenalectomized animal. In neither is there evidence from the blood specific gravity data of a gross leakage of plasma. Unfortunately, our adrenalectomized dogs given diphenhydramine also showed a fall in central venous pressure, which was corrected only some time after the infusion was over. A decline in cardiac index did not accompany the fall in venous pressure in this case.

It is not clear, however, that diphenhydramine prevented the peripheral dilation which is commonly regarded as the most important factor in the acute circulatory crisis produced by administered histamine. Actually, the dose used could reduce but not prevent the fall in both arterial and venous pressures seen in nonadrenalectomized animals given the infusion of histamine. Further, the diphenhydramine treated adrenalectomized dog given plasma showed evidence of a peripheral dilatation, therefore little clue to the nature of the protective action of this drug against the fulminating collapse following plasma can be obtained from the evidence presented. We can only speculate on whether an "antihistaminic" or some other pharmacologic action of the drug is involved.

SUMMARY

The administration of 120 ml. of aseptically collected normal dog plasma, at a rate of 4 ml./min., was always fatal to adrenalectomized dogs on maintenance desoxycorticosterone acetate therapy. The cardinal features of this reaction were a general restlessness, a rather rapid fall in arterial pressure and in cardiac index, a decline in central venous pressure, and general prostration. Most dogs developed a bloody diarrhea. A minority showed edematous swelling of the face with
itching. Animals with intact spleens showed marked hemoconcentration. A similar cell fraction change was not seen in splenectomized-adrenalectomized dogs. Blood and plasma specific gravity determinations offered no evidence of gross plasma loss, or of any large movement of ultrafiltrate. The fatal collapse could be prevented by pretreatment with diphenhydramine. This drug also produced a reversal of the circulatory collapse when given after the infusion. Animals protected by diphenhydramine still showed a fall in venous pressure, but not in arterial pressure. The cardiac index was elevated. The plasma gave no depressor reaction in non-adrenalectomized dogs, but rather a small pressor response.

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