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THE BLOOD-PRESSURE RAISING SECRETION OF THE ISCHAEMIC KIDNEY

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The co-existence of arterial hypertension and renal lesions has been observed for a long time. This fact has induced many investigators to attempt the production of arterial hypertension by experimental modification of the kidney. The methods used have been numerous and varied, e.g. surgical removal of part of the kidney, ligature of the renal artery or some of its branches, reduction of the calibre of the renal vein, ligature of the ureter, multiple emboli of the kidney, irradiation of the kidney, toxic nephritis, renal compression, etc. References to the principal experiments of this nature can be found in the articles by Braun-Menéndez [1932], Goldblatt [1937] and Fasciolo [1938*b*].

In 1927, with Biasotti, experiments were done on partial removal of the kidney, and in 1933 with Braun-Menéndez on partial occlusion of the renal vein in the dog, but hypertension so obtained was generally inconstant and transient, therefore the experiments were discontinued. Eventually satisfactory and constant results were obtained using the technique of Goldblatt, Lynch, Hanzal & Sumerville [1934], compressing the renal artery and reducing its calibre by means of an adjustable forceps, which caused renal ischaemia and permanent hypertension with 50–100 mm. Hg rise above the initial blood pressure. The arterial tension generally rose from an initial level of 130–140 to 180–250 mm. Hg; 185 animals thus treated were studied.

Compression of the splenic or femoral arteries [Goldblatt *et al.* 1934] or the mesenteric or coeliac arteries [Houssay & Fasciolo, 1937*b*, 1938] did not produce hypertension; that of the coeliac trunk produced a gradual hypotension in two cases.

The arterial tension was measured directly by arterial puncture or with Van Leersum's arterial loop or the indirect technique of Biasotti. In the end the first was the principal method used.

Arterial hypertension due to renal ischaemia

Rise in blood pressure is obtained when ischaemia of either or both kidneys is produced. If only one kidney is involved the blood pressure usually increases less and more slowly than if the two are involved; moreover, after a time it has a tendency to fall gradually to the normal level [Loesch, 1933; Goldblatt *et al.* 1934; Elaut, 1936; Houssay & Fasciolo, 1937*a*, *b*, etc.].

Ischaemia of the kidney is the cause of hypertension, since on removal of a unilaterally treated kidney the raised blood pressure rapidly falls to normal, as shown by Goldblatt *et al.* [1934], Dicker [1937*a*], Houssay & Fasciolo [1937*a*]. This is also shown by the fact that on removal of the forceps causing compression of the renal artery the blood pressure returns to normal [Dicker, 1937*a*; Goldblatt, 1937].

The hypertension is not due to uraemia, since in many animals with high blood pressure the blood urea is normal. Also, when bilateral nephrectomy is performed, there is a fall in the arterial pressure 40 hr. later [Houssay & Taquini, 1938], a fact which is already well known.

Role of the nervous system

The hypertension is not caused by a reflex starting from the kidney, since it can be produced and maintained after large resections of the nervous vasoconstrictor system. The hypertension produced by renal ischaemia is not prevented or cured by renal denervation [Page, 1935; Collins, 1936; Goldblatt, 1937] or section of the splanchnic nerves even when associated with removal of the last four thoracic sympathetic ganglia [Goldblatt, Cross & Hanzal, 1937]. Neither is it cured by section of the anterior roots from the sixth dorsal to the second lumbar [Goldblatt & Wartman, 1937], nor by complete removal of the sympathetic chains [Freeman & Page, 1937; Heymans, Bouckaert, Elaut, Bayless & Samaan, 1937; Alpert, Alving & Grimson, 1937]. It is also not prevented by bilateral section of the splanchnic nerves and the sympathetic lumbar chains [Introzzi, Canonico & Taiana, 1938]. Because of these results Goldblatt [1937] states: "this type of experimental hypertension is due primarily to a humoral and not to a nervous mechanism initiated by the ischaemia of the kidney."

Kidney extracts

Unsatisfactory results have been obtained by efforts to demonstrate the existence of a substance producing renal hypertension in extracts of ischaemic kidneys; besides it would be more interesting to know what is

produced and excreted into the blood than what is stored in the parenchyma.

Tigerstedt [1897] and Tigerstedt & Bergmann [1898*a*, *b*] have pointed out that extracts of normal kidney have a hypertension producing action, and this has been confirmed by others. Recently two groups of investigators, Harrison, Blalock & Mason [1936], on the one hand, and Prinzmetal & Friedman [1936] on the other, have made a comparative study of the action of normal kidney extracts and extracts of ischaemic kidneys. Extract of normal dog's kidney, when injected intravenously in dogs, produces an initial drop in arterial blood pressure followed by a gradual and prolonged rise which lasts 10–30 min. or more. Extract of ischaemic kidney produces usually less initial drop and a larger secondary increase than that of normal kidney. Prinzmetal & Friedman say that these results are compatible with the theory that the hypertension can be due to an excess of a blood pressure raising substance normally present in the kidney, but that the data are not sufficient to establish a causal relationship between the blood pressure raising substance of the kidney and the arterial blood pressure. Recently Harrison, Blalock, Mason & Williams [1937] have tried the extracts on rats anaesthetized with pentobarbital because these animals do not react with the initial hypotension. Extracts of kidneys from six dogs with hypertension caused a larger increase in blood pressure than extracts of kidneys from five normal dogs.

Ischaemic kidney graft

Houssay & Fasciolo [1937*a*] grafted an ischaemic kidney in the neck of a chloralosed dog, uniting the artery to the carotid and the renal vein to the jugular; this was done by means of Payr's canulae, one of which connected the carotid with the aortic opening of the renal artery and the other connected the jugular with the renal vein (Fig. 1). The dog which received the graft was previously nephrectomized and its arterial blood pressure recorded during 2 hr. At the end of this time the donor was anaesthetized with ether or chloralose and the kidneys removed and then grafted into the receptor, the operation being completed in from 5 to 15 min.

Using this technique twenty-four kidneys in which the renal arteries had been compressed from 3 to 40 days, provided by twenty-four dogs with raised blood pressure (between 175 and 210 mm. of mercury), were grafted into thirty receptors.

When the blood flowed from the carotid through the graft and was seen to return by the renal vein, the blood pressure rose rapidly, rising

by 32–70 mm. Hg in 5–10 min. Later it remained stable at this figure or slightly lower (Figs. 2 and 3).

If the grafted kidney was removed and placed in the neck of another dog, this in its turn had a rise in blood pressure; meanwhile the blood pressure of the first dog fell slightly, but sometimes not at all, during the first 20–30 min., and remained high for several hours. When the kidney was regrafted a second time into the first dog the blood pressure increased little or not at all when it was already high due to the first grafting.

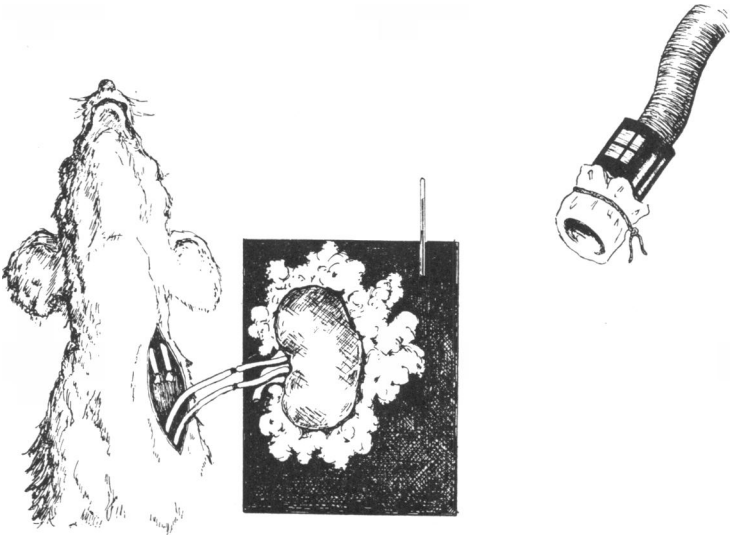

Fig. 1. Kidney grafted into the neck by arterial and venous anastomosis. Above, a vessel with a Payr's canula.

In the graph of Fig. 4 the rise in blood pressure obtained in sixteen out of seventeen dogs is shown. Such a rise was seen in twenty-seven of the thirty grafted dogs. In two of the three negative experiments the kidneys were each grafted with good result in one dog, in the third the ischaemic kidney did not cause a rise of blood pressure in a resistant dog, but did so when grafted in another animal.

In the same way twenty-five kidneys obtained from twenty-two normal dogs were grafted into the necks of twenty-seven chloralosed, recently nephrectomized dogs (Fig. 5). The kidneys from nineteen dogs did not produce any rise in blood pressure after grafting. The kidneys of three dogs produced rises of 20, 39, 45 and 70 mm. Hg. In the last experiment one kidney produced a significant rise of blood pressure in two dogs,

the blood pressure rising in one from 125 to 195 and in the other from 140 to 185 mm. Hg. Unfortunately there was no histological examination to prove whether or not the kidneys were really healthy. In three cases the

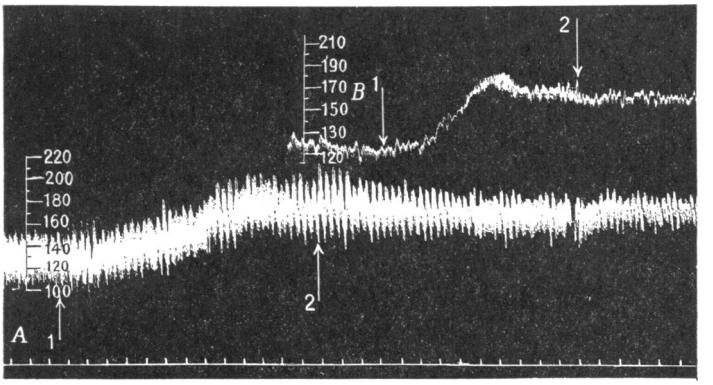

Fig. 2. Graft of an ischaemic kidney from a dog with high blood pressure (200 mm. Hg) into two nephrectomized chloralosed dogs. A, Dog. 12·5 kg. 1, graft placed in neck; 2, graft withdrawn. B, Dog 11·0 kg. 1, graft placed in neck; 2, graft withdrawn.

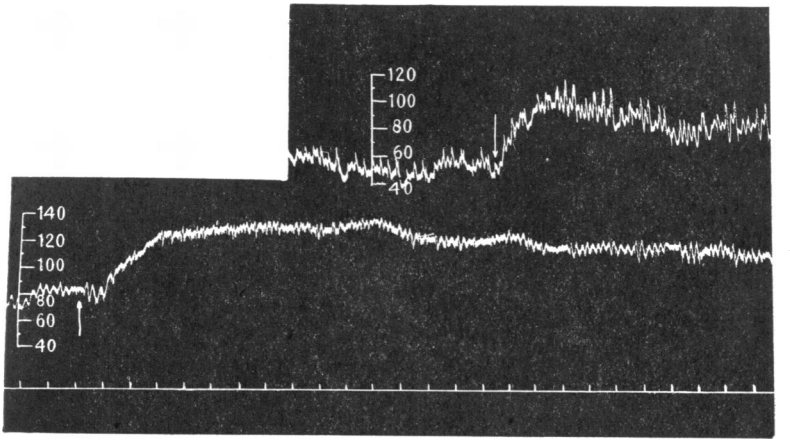

Fig. 3. Similar experiment to that of Fig. 2. Ischaemic kidney from a dog with raised blood pressure; the arrows mark when it was grafted into the neck, first in one and then in another chloralosed nephrectomized dog.

normal kidneys were removed and left between 30 and 45 min. at room temperature and then regrafted, but even so there was no rise in blood pressure.

Comparative grafts of the ischaemic and healthy kidneys of animals operated on one side only were performed. While the ischaemic kidney

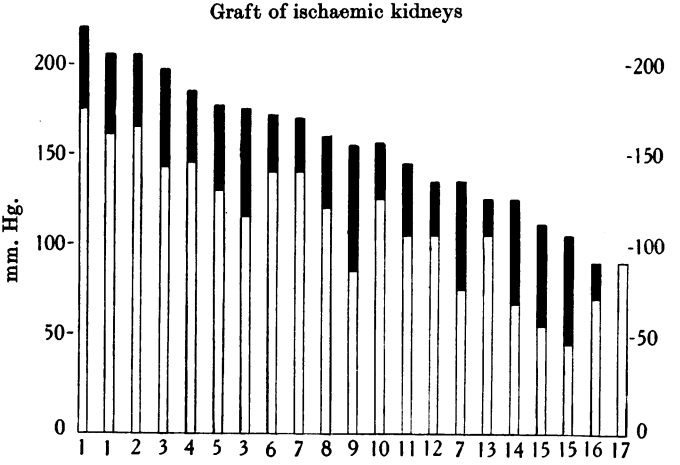

Fig. 4. Each column is an experiment with an ischaemic kidney from a dog with raised blood pressure (180–210 mm. Hg) grafted into the neck of a chloralosed nephrectomized dog. The white column indicates the initial level of the blood pressure, the black the increase produced by the graft. The lower numbers correspond to the record numbers of the dogs.

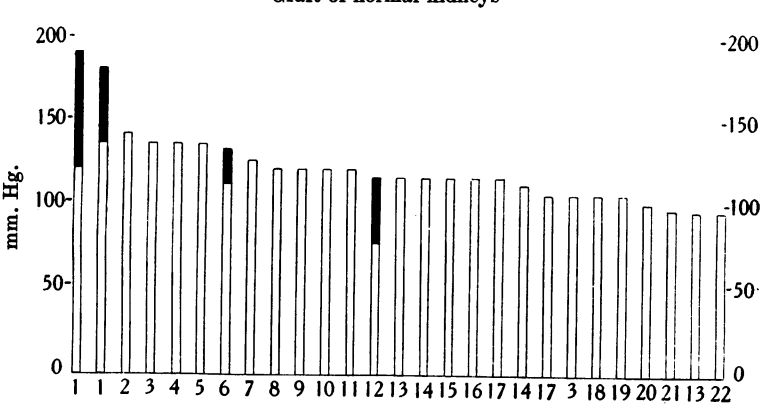

Fig. 5. Each column represents an experiment with the graft of a normal kidney into the neck of a chloralosed nephrectomized dog. The white column indicates the initial blood pressure, the black the increase produced by the graft. The lower numbers correspond to the record numbers of the dogs.

always produced a rise in blood pressure the healthy kidney usually did not. Nevertheless, in one case the healthy kidney produced a rise in blood pressure which presently became stable; when this occurred the kidney was

removed and the ischaemic kidney grafted instead, producing a further rise in blood pressure; this seems to demonstrate that the ischaemic kidney produces a more active substance than the healthy one.

In one case the kidney had two renal arteries, one of which was compressed. This kidney was grafted by anastomosing first the untouched artery; this did not produce a rise in blood pressure. The kidney was then connected by the compressed artery, and this produced a rise in blood pressure. Each time the kidney was grafted it was possible to see perfectly marked out the areas supplied by each of the two arteries.

These experiments show that the ischaemic kidney induces hypertension in the dog by producing a secretion which causes a rise of the normal blood pressure till it reaches hypertension level and maintains it there.

Dicker [1937*b*] has confirmed the fact that a kidney grafted into the neck of a normal dog can cause a rise in arterial blood pressure.

The vasoconstrictor substance is produced by a secretion of the ischaemic kidney and not by an autolysis of the organ, since its action is maintained during months and at autopsy the organ may present good size and appearance.

Action of the venous blood of the ischaemic kidney

Comparative studies have been made [Houssay & Taquini, 1938] on the vasoconstrictor action of the plasma of venous blood from both healthy and ischaemic kidneys. The blood of chloralosed animals was collected and mixed with an equal volume of Ringer's fluid with 4 % sodium citrate, it was rapidly centrifuged and the plasma diluted to a quarter strength with Ringer's fluid. In this way plasma, containing 0·5 % of citrate and diluted with calcium-free Ringer's fluid to eight times its original volume, was finally obtained.

The vasoconstrictor action of these plasmas was tested by Laewen-Trendelenburg's method in the toad *Bufo arenarum* Hensel. The efferent drops of the preparation were electrically registered together with the time in minutes. A special apparatus allowed the perfusion to take place at a constant pressure of 15–25 cm. of water, and the liquids were easily changed without modifying the pressure.

First, Ringer's solution was perfused for at least ½ hr., till a constant outflow was obtained, one plasma was then perfused for 20 min., then replaced by Ringer, and, finally, the other plasma was perfused. In one toad the venous blood from a normal kidney was first perfused and in another the venous blood from the ischaemic kidney of a dog with raised blood pressure.

The venous blood plasma from ischaemic kidney always had an intense vasoconstrictor action (Fig. 6) which began immediately, increased for several minutes and then remained steady (Fig. 7). When Ringer's fluid

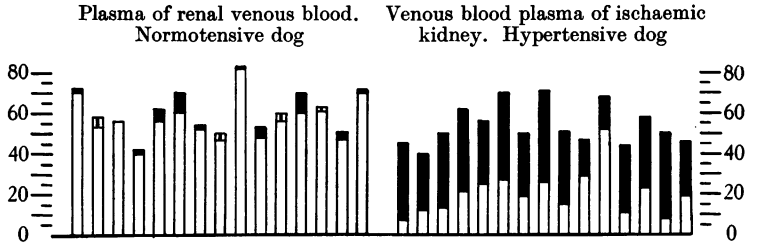

Fig. 6. Vasoconstrictor action of citrated blood plasma in a vascular preparation of a toad according to the Laewen-Trendelenburg method. Each column corresponds to one plasma; the height indicates the initial number of efferent drops from the preparation perfused with Ringer's solution. The decrease in drops is indicated by the black columns, the increase by the striped columns.

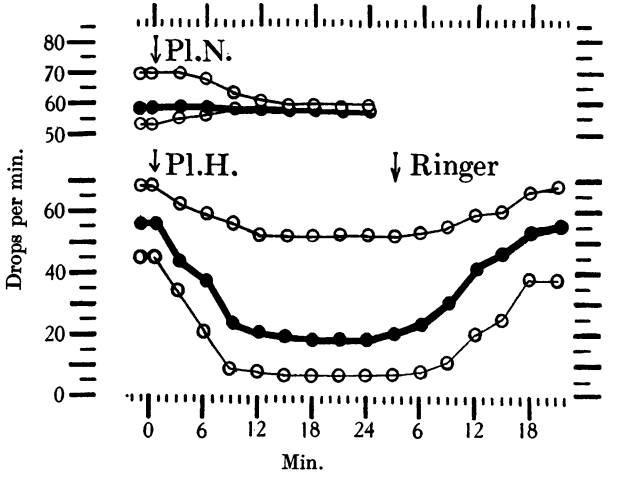

Fig. 7. Vascular preparations of toads according to the Laewen-Trendelenburg method. Number of drops per min. Pl.H., plasma from venous blood of ischaemic kidneys (high blood pressure); Pl.N., venous blood plasma from normal kidneys. The thin line is the largest and smallest constriction with each type of plasma. The thick line is the average action of the plasma from fifteen dogs.

was perfused later the vasoconstrictor effect gradually disappeared. The renal venous plasma from fifteen dogs with hypertension tried in twenty toads decreased the initial number of drops by 63 %, the maximum decrease being 84·5 % and the minimum 18·5 %.

The venous blood plasma from the normal kidney of fifteen dogs was

little or not at all active. There was a slight decrease in the number of drops in nine cases, a slight increase in five and no alteration in one. The maximum decrease was 9·4 % and the average 2·8 %.

The vasoconstrictor action is not due to uraemia, it occurs with the renal plasma of dogs with hypertension in which the blood urea is normal.

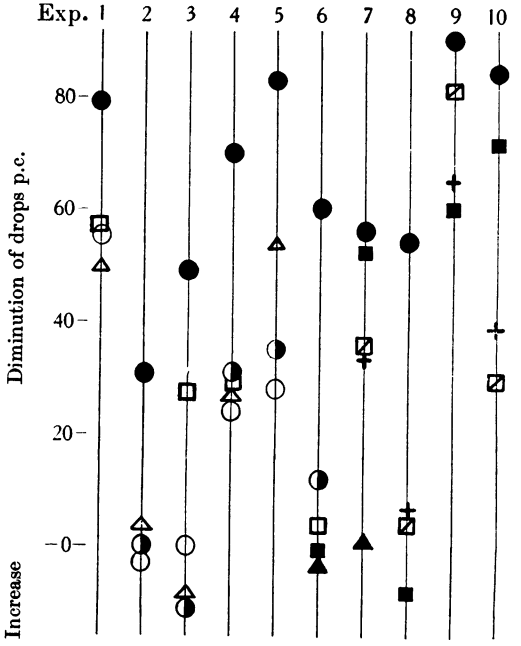

Fig. 8. Surviving vascular system of the toad *Bufo arenarum* Hensel (Laewen-Trendelenburg method). Percentage diminution of drops (vasoconstriction) or augmentation of drops (vasodilatation), produced by the plasmas (diluted 1 : 10 and citrated to 0·4 p.c.) from venous blood of different organs of hypertensive dogs. The hypertension was produced by renal ischaemia of the only remaining kidney. Each vertical line corresponds to one dog.

○ Vena jugularis pl. ◑ Carotis comm. pl. △ Lienal v. pl.
▲ Hind leg pl. ■ Hepatic v. pl. \+ Right heart pl.
▨ Left heart pl. ● Renal pl. □ Mesenteric v. pl.

It was also shown that 40 hr. after bilateral nephrectomy the blood plasma from the right heart of five uraemic dogs did not give a vasoconstrictor action.

These experiments show that the ischaemic kidney produces a substance with an intense direct vasoconstrictor action. The vasoconstrictor action is not seen with the ultrafiltrate of the citrated plasma using acetic collodion membranes nor when the plasma is deproteinized according to the method of Folin & Wu.

Houssay & Taquini [1938] have compared the action of venous blood plasma from the different organs of ten animals with hypertension of renal origin. The venous blood from the ischaemic kidney and from three to five different organs was collected, avoiding asphyxia and taking care to reduce reflexes to a minimum.

In all cases the venous blood plasma from the ischaemic kidney caused a higher vasoconstrictor action than any other blood (Fig. 8). The blood from the carotid, right and left hearts, splenic, mesenteric, hepatic and femoral veins have all been studied separately, and these experiments all show that the ischaemic kidney is the essential or only site for the production of a vasoconstrictor substance in the dog with hypertension. This substance accumulates in the blood to a certain extent and appears to be destroyed in certain organs, the healthy kidney being specially active, as will be seen later.

The protecting role of the healthy kidney

Healthy renal tissue eliminates or destroys in a varying degree the vasoconstrictor substance. This has been shown by the various experiments of Fasciolo [1938*a*, *b*].

(1) Extirpation of one kidney does not produce a rise in blood pressure. If 8 or 10 days later the artery of the remaining kidney is compressed, the blood pressure rapidly rises and is maintained at a high level with oscillations. In animals which were observed for 6 months the blood pressure was maintained at 220–250 mm. Hg from the 40th day after the operation. If the renal artery of one kidney is compressed, the other remaining intact, the rise in blood pressure is less rapid and is not always maintained. In most cases the blood pressure returns to normal.

In a series of eighteen dogs having a single ischaemic kidney there was an average rise in blood pressure of 11·7 mm. Hg per day, while in a series of twenty-three dogs with one ischaemic kidney and the other intact, the average rise was 5·2 mm. Hg per day. In the dogs with the single ischaemic kidney the average rise was 47 mm. at the 4th day, while in those which had a healthy kidney as well the average rise was only 37 mm. in 7 days.

(2) If the healthy kidney in the dogs with one ischaemic kidney is removed when the blood pressure is stable or declining, the blood pressure rapidly rises to a high level and is maintained there. The average increase was 28 mm. for eight dogs 7 days after the one kidney had been made ischaemic, at the 17th day the increase had declined to 18 mm. The healthy kidney was then removed, and in 8 days only the increase was 60 mm. Hg, giving a blood pressure of 200 mm.

(3) Grafting of the ischaemic kidney of a dog with hypertension in the neck of another dog caused a greater increase in nephrectomized animals than in those which had their kidneys. The average rise in seven comparative experiments was 32 mm. Hg in the nephrectomized animals and 4 mm. in animals with kidneys intact.

(4) When on one side the kidney has been made ischaemic, its venous blood has a potent vasoconstrictor action, which is greater than that of the general blood stream. On the other hand, the blood which leaves the healthy kidney can show a marked reduction of this action compared with the blood which supplies it.

All these experiments show that the normal kidney is capable of reducing the rise in blood pressure produced by the ischaemic kidney.

Role of the endocrine glands in hypertension of renal origin

Page & Sweet [1937] have observed that the rise in blood pressure due to renal ischaemia can occur, but is not maintained, in absence of the hypophysis. We have obtained increases to 170 and 195 mm. Hg starting from 120–140 mm. According to Page & Sweet the rise is produced but is less marked and transitory, particularly if there is adiposity or a low basal metabolism. Hypophysectomy carried out in dogs with hypertension causes a reduction of the blood pressure to the normal level or slightly higher than normal in 20 days. Page & Sweet say that "the effect of hypophysectomy on hypertensive dogs is believed to be an indirect one. It is postulated that the responsiveness of the blood vessels to chemical stimuli from the kidneys with constricted renal arteries is reduced. This may be due to lack of the secretions of the adrenal and thyroid glands. Deficiency of these secretions may in turn be due to withdrawal by hypophysectomy of the chemical stimuli normally afforded them by the hypophysis."

Thyroidectomy neither prevents nor cures the arterial hypertension due to ischaemia of the kidney [Glenn & Lascher, 1938].

Extirpation of the right adrenal and the left adrenal medulla, with or without section of the splanchnic nerves, does not prevent hypertension from being produced by the ischaemic kidney [Goldblatt *et al.* 1934; Fasciolo, 1938*a*, *b*]. It is only necessary to leave a small piece of adrenal cortex for the blood pressure to rise and remain high [Goldblatt, 1937].

The role of the adrenal has been studied by Goldblatt [1937]. Bilateral extirpation of the gland prevents the rise in blood pressure or

causes it to drop if it has already risen. This has been observed also in various animals kept alive for several months with sodium salt treatment. Nevertheless, in two cases the blood pressure rose under these conditions. Extract of the cortex caused the blood pressure to rise.

Introzzi *et al.* [1938] have observed that the blood pressure in dogs with hypertension drops, sometimes to normal, after resection of the splanchnic nerves and the lumbar sympathetic chains and a large part of the adrenals, but these observations only lasted for 40–60 days.

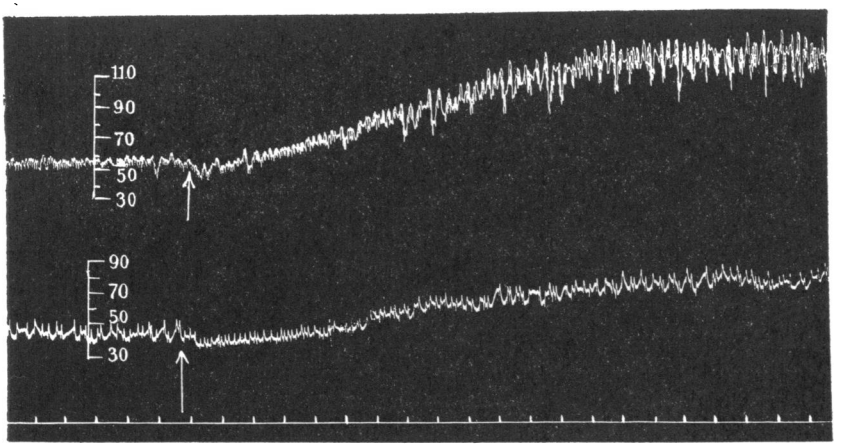

Fig. 9. The arrow indicates the grafting of the ischaemic kidney from two hypertensive dogs into the neck of two adrenalectomized and nephrectomized dogs.

Fasciolo [1938*a*, *b*] has shown that grafting the ischaemic kidney of a dog with hypertension produces the same rise in blood pressure in chloralosed nephrectomized dogs whether they have adrenals or not. The average rise in six comparative experiments was 26–30 mm. Hg respectively. In the graph (Fig. 9) it can be clearly seen that the vasoconstrictor substance secreted by the grafted ischaemic kidney produced its blood pressure raising effect independently of the adrenals.

The right adrenal was removed in chloralosed dogs and the adrenal veins temporarily compressed; an ischaemic kidney from a dog with hypertension was grafted into the neck and the blood pressure rose in three cases. When the blood pressure remained stable the forceps were removed from the adrenal veins, but the blood pressure did not rise [Fasciolo, 1938*a*, *b*]. Therefore the substance causing hypertension produced by the ischaemic kidney does not act through the adrenal.

The results obtained by Goldblatt can probably be explained because cortin favours the production of hypertension either by increasing the formation of the vasoconstrictor substance by the kidney or perhaps by increasing the sensitivity of the vasomotor system to its action.

For reasons of space the visible and histological changes observed in the animals with hypertension as well as other interesting points have not been discussed.

SUMMARY

Evidence is presented that the ischaemic kidney secretes directly a vasoconstrictor substance which causes a permanent hypertension. This substance is active in the absence of the adrenals. The healthy kidney is capable of diminishing the action of this blood-pressure raising substance.

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