man thermometer in the usual manner. When the rate had been constant for at least 4 5-minute periods, posterior pituitary extract was given intravenously, in amounts of the order of 0.04 International Units per kg body weight.

As in the previous study, this amount of pituitary was followed almost invariably by an increase in both rate and chloride content. Sucrose determinations were not made, but in the previous series it invariably fell. Specific gravity either fell or remained constant, and the freezing point remained practically constant. The results, which were consistent throughout, are illustrated in the record of a single experiment shown in Fig. 1.

Conclusions. The finding that the osmotic concentration, as revealed by the depression of the freezing point, remains constant during the action of pituitary extract on the diuresis induced by rapid intravenous infusion of sucrose solutions, lends support to the view that the absorption capacity of the tubules has been reached under these conditions of experiment.

11306

Etiology of Hypertension Due to Complete Renal Ischemia.

MYRON PRINZMETAL,* HARVEY LEWIS AND SIDNEY LEO.† (Introduced by Ella H. Fishberg.)

From the University of Southern California Medical School.

It is generally agreed that the hypertension which develops in experimental animals as a result of partial[1] or complete[2] ischemia of the kidneys is of humoral and not of nervous origin.

Although *renin,* a pressor extract prepared from the renal cortex, has been implicated by some observers,[3, 4] neither this product nor any other has to date been proved to be the substance responsible for ischemic hypertension.

---

* Dazian Fellow.

† Beaumont Research Fellow.

1 Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W., *J. Exp. Med.*, 1934, **59**, 347.

2 Taquini, A. C., *Rev. Soc. argent. de biol.*, 1938, **14**, 422.

3 Prinzmetal, M., and Friedman, B., PROC. SOC. EXP. BIOL. AND MED., 1936, **35**, 122.

4 Harrison, T. R., Blalock, A., and Mason, M. F., PROC. SOC. EXP. BIOL. AND MED., 1936, **35**, 38.

In this communication we wish to report the finding of a perfusate of ischemic kidneys which causes the elevation of blood pressure following the release of complete renal ischemia. Until the precise nature of the active principle has been determined, we propose the name *ischemin,* which may be defined as the pressor substance contained in perfusates of completely ischemic kidneys and which is responsible for the hypertension resulting from the release of total renal ischemia. For convenience, the renal perfusate containing the pressor substance will also be termed *ischemin.*

The results of the observations made thus far are summarized briefly.

In 8 experiments, cats were anesthetized with ether and the renal pedicle of one kidney clamped. After 4 to 6 hours the animal was reanesthetized with nembutal, the blood pressure recorded from the carotid artery, and both the normal and ischemic kidneys removed. Within 5 minutes following the removal of the kidneys, both renal arteries were cannulated and the kidneys perfused with 1 cc of warm saline per gram of kidney. The perfusates were then injected intravenously into the same animal. The perfusates of the ischemic kidneys uniformly gave a marked and prolonged rise in blood pressure, amounting to as much as 100 mm of Hg, whereas those obtained from the normal kidneys had no pressor effect.

Perfusates of ischemic hind limbs of cats were found to contain no pressor substance.

The first series of experiments having demonstrated the presence of pressor material *(ischemin)* in perfusates of ischemic kidneys, it was decided to determine whether this substance was responsible for the hypertension resulting from the release of complete renal ischemia (Taquini[2]). If *ischemin* causes this rise in blood pressure, there would necessarily be less *ischemin* in the perfusate of the kidney, the circulation of which has been reëstablished than in a control ischemic kidney in which the circulation has not been reëstablished. For this reason the following experiment was devised:

Both renal pedicles of 22 cats were clamped under ether anesthesia. After 4 to 6 hours, the animals were reanesthetized, with nembutal and the blood pressure recorded from the carotid artery. In each instance, upon reëstablishing the circulation of one kidney, the usual rise in blood pressure took place.[2] The other kidney was not unclamped. Fifteen minutes later both kidneys were removed and perfused in the manner previously described. The perfusate of the released kidney was injected intravenously into the same animal, followed after a suitable interval by the perfusate of the unreleased kidney.

It was found that the perfusate of the unreleased kidney showed a significantly greater pressor effect than that of the released kidney, the average rise in blood pressure being 33 mm and 16 mm of Hg, respectively.

The smaller pressor response of the perfusate of the released kidney, as compared with that of the unreleased kidney, is readily explained by the washing out into the general circulation of some (or all) of the *ischemin* from the released kidney upon removal of the clamp.

The perfusate of the released kidney was intentionally injected first, because of the phenomenon of tachyphylaxis (see *ischemin* characteristics a). Except for this phenomenon, the difference in pressor response would have been considerably greater.

Additional evidence that *ischemin* is the substance responsible for the hypertension occurring after reëstablishment of the circulation of completely ischemic kidneys follows:

1. 933F (piperidomethyl-3-benzodioxane) does not reverse the rise in blood pressure following reëstablishment of the circulation of completely ischemic kidneys or the pressor response to *ischemin.*

2. The blood pressure curve following reëstablishment of the circulation of completely ischemic kidneys is similar to that produced by intravenous injection of *ischemin.*

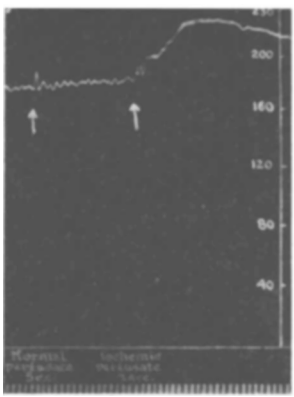

FIG. A.

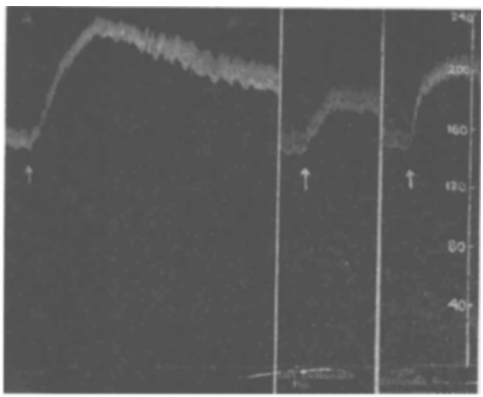

FIG. B.

FIG. A.

At first arrow, intravenous injection of perfusate of normal right cat's kidney. At second arrow, injection of perfusate of same animal's left kidney rendered completely ischemic for 5 hours.

FIG. B.

Five hours previously, both renal pedicles clamped. At first arrow, clamp removed from left renal pedicle. At second arrow, intravenous injection of perfusate of left (released) kidney. At third arrow, injection of perfusate of right (unreleased) kidney.

Nembutal anesthesia. Time 15-second intervals.

TABLE I.

Time	Pressor effect
3:24	40 mm Hg
3:50	32
4:17	28
4:27	24
4:33	14
4:43	14
5:05	12

The amount of *renin* in extracts of normal, unreleased ischemic, and released ischemic kidneys is now being investigated.

Ischemin exhibits the following characteristics:

a. Tachyphylaxis. By this is meant that repeated injections of a pressor substance into the same animal cause decreasing effects. An example in the case of *ischemin* is shown in Table I.

b. The boiling of *ischemin* for 5 minutes destroys the active pressor principle.

c. The action of *ischemin* is not reversed by 933F (piperidomethyl-3-benzodioxane).

From these experiments it is concluded that as a result of complete renal ischemia, pressor material *(ischemin)* accumulates in the kidney and is readily washed out into the general circulation when the renal blood flow is reëstablished or by artificial perfusion of the extirpated organ. This is the first time a pressor substance has been obtained which has been proved to be the cause of hypertension due to renal ischemia.

This substance *(ischemin)* has certain properties in common with *renin:* destruction by heat, similar character of the pressor curves, the property of tachyphylaxis, and failure of 933F to abolish the pressor reaction,[5] but until decisive physiological and chemical studies have been performed, no definite statement should be made concerning the relationship of these two products, nor to the heat-stable renal pressor substance which has recently been described.[6]

[5] Katz, L. N., and Friedberg, L., *Am. J. Physiol.*, 1939, **127**, 27.

[6] Victor, J., Steiner, A., and Weeks, D. M., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 767.