Evidence for Renotrophin as a Causal Factor in Renal Hypertension

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Most of the methods used for the production of experimental renal hypertension involve a reduction in the amount of functional renal tissue. According to the renotrophin hypothesis, the blood pressure of animals with experimental hypertension should be reduced or normalized if the rate of production of renotrophin is reduced (hypophysectomy, thyroidectomy, low protein diet) or if the functional renal mass is increased (kidney transplant, parabiosis). Conversely, the blood pressure should rise to higher levels or hypertension develop if the rate of production of renotrophin is increased (thyroid hormones, somatotrophin, testosterone, thyrotrophin, gonadotrophin in males, protein-rich diets) or if the functional renal mass is further reduced (sensitizing actions of unilateral nephrectomy, etc.). Experimental evidence to be presented conforms with the renotrophin hypothesis and its 4 corollaries.

SOME years ago I proposed a working hypothesis that may be expressed as follows: The size of the kidney and its functional capacity, which in normal conditions are more or less closely connected, would be determined by the concentration in the blood of one or various substances (probably some intermediary product of protein metabolism) which the kidney must eliminate, or more probably destroy, utilize or transform.\textsuperscript{1,2} When the production of these kidney growth stimulating substances, which for greater convenience we designated renotrophin, is increased, the kidney enlarges in size and in function until a new equilibrium is reached between production and destruction, utilization, or transformation of the substances. Thus, when a protein-rich diet, pituitary extracts, testosterone, or thyroid hormones are administered, factors which increase the production of renotrophin, the kidneys increase in size and function. When the administration of these factors is suspended, the kidneys regain their previous normal weight. Contrariwise a low protein diet, hypophysectomy, or thyroidectomy cause a reduction in renal weight and function because of a lesser production of renotrophin by the organism (fig. 1). If the nutritional and hormonal conditions are kept constant and the amount of renal substance is artificially reduced (unilateral nephrectomy, partial nephrectomy, induced renal lesions, etc.), the concentration of renotrophin should increase, stimulating the growth of the remaining kidney tissue and increasing its function until the equilibrium between formation and destruction of renotrophin is re-established.

According to this theory, hypertension develops when this equilibrium is broken and the remaining renal tissue is unable to respond to the stimulus of the normal or increased amount of renotrophin present in blood. It is well known that practically all the methods used for the production of experimental renal hypertension involve a reduction in the amount of functional renal tissue with or without a concomitant increase in the rate of production of renotrophin. A discussion of the various experimental conditions in which hypertension is the result of a disequilibrium between renotrophin production and its destruction by the kidney has previously been published.\textsuperscript{1,2}

According to the renotrophin hypothesis, the blood pressure of animals with experimental renal hypertension should be reduced or normalized if (1) the rate of renotrophin production is reduced, or (2) the functional

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RENOTROPHIN AS A CAUSE OF HYPERTENSION

renal mass is increased. Conversely, the blood pressure should rise to higher levels or hypertension, if still absent, should appear, if (3) the rate of production of renotrophin is increased, or (4) the functional renal mass is further reduced. We shall present some experimental evidence for each of these 4 corollaries.

Reduction of Rate of Renotrophin Production. Hypophysectomy causes a fall of blood pressure in hypertensive dogs\(^3\) \(^4\) and rats,\(^5\)-\(^8\) but if it is performed a month or more before the renal arteries are constricted, it does not prevent the development of experimental renal hypertension.\(^9\) \(^9\) \(^10\) On one hand, the presence of the anterior lobe of the hypophysis seems indispensable to maintain renal hypertension; on the other hand, previous hypophysectomy does not prevent the hypertension resulting from constriction of the renal arteries. This apparent contradiction is well explained by the renotrophin hypothesis. In the animal rendered hypertensive by reduction of renal mass, hypophysectomy causes a reduction in the rate of production of renotrophin; the disequilibrium previously existent disappears and with it the rise in blood pressure. In the normal animal, hypophysectomy causes a reduction in renotrophin production and with it a parallel reduction in

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**Fig. 1** Top. Schematic representation of renotrophin hypothesis.

**Fig. 2** Bottom. Schematic representation of effect of hypophysectomy on blood pressure of hypertensive dogs. Height of rectangles represents renotrophin production. (Reprinted from Cardiologia 21: 272, 1952.)
renal functional mass. But if we further reduce the latter by constriction of the renal arteries or increase the former by thyroid administration, the imbalance is the same as in an intact animal and hypertension develops (fig. 2).

A low protein diet lowers the blood pressure of rats with hypertension due to reduction of renal mass.1

Symptoms and manifestations of hypothyroidism following thyroidectomy are less pronounced in the dog than in the rat. This is probably the reason why thyroidectomy in dogs does not prevent or cure hypertension produced by constriction of the renal arteries.11-13 As extirpation of the thyroid in the rats and other nephrectomy (RN). Administration in administration, reduce renal (broken lines) and (fig. 1). Signs and other nephrectomized dogs than the intact animal or the other (fig. 3). On the other hand, thioracil or I131 administration in rats with a ligated kidney prevented the hypertension which usually follows removal of the contralateral kidney (fig. 4). Other authors have obtained similar results in other types of experimental hypertension.15-18, 26

Increase of Renal Functional Mass. The vascular transplant of a normal kidney

FIG. 3 Top. Blood pressure of a rat with a figure-eight ligature of the left kidney (LLK) and right nephrectomy (RN). Administration of 875 μc of I131 caused a return to normal blood pressure. Time, months.

FIG. 4 Bottom. Blood pressure of 2 groups of 10 rats each with figure-eight ligation of the left kidney (LLK) and right nephrectomy (RN). One group (broken lines) was injected with I131 (875 μc), the other group (solid line) was kept as a control.

FIG. 5. Effect of parabiosis on the blood pressure. Parabiosis between a totally nephrectomized rat and a normal rat. The blood pressure of the nephrectomized rat may rise to hypertensive levels; hypertrophy of the kidneys of the normal rat (upper pair). Parabiosis between a hypertensive rat and a normal one causes the blood pressure of the former to return to normal levels (middle pair). No significant blood pressure fall occurs if a hypertensive rat is united in parabiosis with another hypertensive rat (lower left pair) or with a nephrectomized rat (lower right pair). (Reprinted from Acta. physiol latinoam. 2: 1, 1952.)
RENOTROPHIN AS A CAUSE OF HYPERTENSION

Fig. 6 Top. Blood pressure of a rat with reduced renal mass. Thyroid powder administration caused a marked increase in blood pressure. (Reprinted from Rev. Soc. Argent. Biol. 30: 138, 1954.)

Fig. 7 Bottom. Two groups of rats were subjected to figure-eight ligation of the left kidney and right nephrectomy. Eight days after operation 1 of the groups (solid line) received daily 50 mg. of triiodothyronine, the other group (broken line) was untreated.

would be the ideal procedure for increasing the renal functional mass. Unfortunately, the problem of renal homotransplantation is not yet solved. Nevertheless, Muirhead\textsuperscript{19} and Kolff and Page\textsuperscript{20} have observed a reduction in blood pressure in dogs with renoprival hypertension a few hours after the vascular transplantation of a normal kidney. The only observations in which the transplant of a normal kidney to a hypertensive subject has been successful (survival of the transplant and normalization of the blood pressure) has, curiously enough, been realized in the human species.\textsuperscript{21}

We have had recourse to parabiosis.\textsuperscript{2} Parabiotic union of a chronically hypertensive rat with a normal rat is followed by a fall in

Fig. 8 Top. Effect of somatotrophin on the blood pressure of a rat with reduced renal mass. (Reprinted from Rev. Soc. Argent. Biol. 31: 95, 1955.)

Fig. 9 Middle. Effect of thyrotrophin on the blood pressure of a group of 4 rats with reduced renal mass compared with 5 control animals. (Reprinted from Rev. Soc. Argent. Biol. 31: 201, 1955.)

Fig. 10 Bottom. Effect of prolonged administration of serum and chorionic gonadotrophins to rats of both sexes. (LLK), figure-eight ligation of left kidney; (RN), right nephrectomy. (Reprinted from Rev. Soc. Argent. Biol. 31: 194, 1955.)
blood pressure to normal levels in the former. This does not occur if the hypertensive rat is united in parabiosis with another hypertensive rat or with a nephrectomized rat (fig. 5). These observations have been confirmed by Masson, Corcoran, and Page.23

**Increased Production of Renotrophin.** In order to study the effect on the blood pressure of factors which increase the rate of production of renotrophin, we have used rats with reduced renal mass which have developed no hypertension or only a mild and irregular form of this disease. These animals which in a state of unstable equilibrium are very sensitive to renotrophic factors. When the growth of the kidney is limited by mechanical impediments or renal lesions such as figure-eight ligature of one kidney and contralateral nephrectomy, they respond readily with elevation of the blood pressure to definite hypertensive levels. We have thus shown that the administration of thyroid hormone,14-33 testosterone, somatotrophin,24 thyrotrophin,25 gonadotrophin in males,26 and protein-rich diets, cause a rapid elevation of the blood pressure to hypertensive levels (figs. 3, 6-10). Other authors have obtained more or less similar results in other types of experimental hypertension.27-30

**Further Reduction of the Renal Mass.** It is important to emphasize that many of the renotrophic factors such as somatotrophin and thyroxin, apart from increasing the rate of production of renotrophin, are able to cause renal lesions, thus further decreasing the functional renal mass.30 Furthermore, DCA or other mineralocorticoids which cause hypertension by different mechanisms, are potentiated in their action by a reduction of renal mass (unilateral nephrectomy, renal lesion, figure-eight ligature) or by the simultaneous administration of renotrophic factors (somatotrophin, thyroid hormones, accelerated body growth). Most of the so-called "sensitizing" conditions mentioned by Selye, including sodium chloride administration fall in one of these categories.31

This working hypothesis has proved its value by its accordance with experimental facts, and its usefulness by opening fruitful lines of inquiry. Its weakest point is the assumption of the existence of a substance (renotrophin) which is still elusive.

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