From a gross morphological point of view, the precipitates α^1 appears as a gelatinous, thick and milky mass, the greater in bulk the more complete has been the dispersion of the fibrils in A. Optical microscopic observation does not reveal any elementary fibrils; in phase contrast the image is practically irresolvable; in dark field a milky diffraction is shown. In a thick drop the gel shows the characteristic birefringent trajectories of collagen.

Under the electron microscope the gel appears formed by a reticulum varying in composition: some zones show a delicate cotton-like appearence consisting of a structure so thin that the single constituents hardly reach the limits of resolution; some other zones show systems of membranes so interconnected that they form a relatively coarse reticulum. Furthermore, some filaments appear clearly spiralized (thickness between 150 and 300 Å). In any case, no structure is normally banded. This gel, however, includes also short, typically banded tactoidal fibers several microns long and as thick as 150–400 Å, with a period ranging from 620 to 690 Å, which show six intraperiodal bands after uranil acetate staining and seven to eight bands after phosphowolframic acid (PTA) staining.

Similar data are obtained for sample β^1, which precipitates on addition of sodium acetate to the B^1 collagen solution. In this case, however, together with a greater amount of fibers of tactoidal shape, many long needle-like filaments, with all the characteristics of native collagen, are observed under the electron microscope. The amount of these fibrils varies from sample to sample, probably in connection with its degree of purity.

The macroscopic appearance of precipitates α^2 and β^2 is closely related to that of samples α^1 and β^1; the sediments, however, are usually contaminated by the presence of small amounts of coarse impurities which settle down easily. Under phase contrast and dark field examination, the presence of filamentous formations, often longer than 20 μ, very similar to the native collagen fibrils, is usually observed in both cases. Polaroscopic and electron microscope investigations confirm the presence of both long fibrils with the characteristic banded structure of native collagen and of a remarkable number of tactoidal fibrils.

Results show that, in spite of the chemical identity of collagen A and of the α^1 precipitate, the morphology of the latter is far from that of typical collagen, whose organization is reproduced in sample α^2 precipitated by means of sodium acetate and by adding mucopolysaccharides. On the contrary, the precipitate β^1 obtained from B^1, whose lesser degree of purity as compared to A^1 is probably due to contamination by polysaccharides from the ground substance of the connective tissue, shows the presence of typically banded collagen fibers. No difference is seen between the electron microscope appearance of the β^1 and β^2 precipitates.

Our data suggest that, on addition of sodium acetate to a pure collagen solution (A^1), a peculiar dispersed gel with a partial molecular arrangement rather close to that of the native collagen precipitates. In this gel one may observe all the stages in the organization of the protein, from unbanded structures to tactoidal fibers showing periodicity, in spite of the lack of regulator mucopolysaccharides.

Therefore, it may be confirmed that collagen protein may aggregate either in the presence or in absence of regulator colloids in several ways, and that the word 'collagen' should define a protein and not a filamentous structure, since the elementary banded fibrils found in the connective tissues are only one of the many para-crystalline states which collagen molecules may assume.

Zusammenfassung. Es wird gezeigt, dass die gelösten Eiweisskörper bei Abwesenheit von Regulierungssubstanzen ein netzförmiges Gel bilden. Dieses enthält Fibrillen ohne periodische Struktur und nadelartige «Tactoïde» mit typischer Periodizität.

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Istituto di Anatomia e Patologia Generale dell'Università di Milano (Italy), February 14, 1962.

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Juxtaglomerular Cells, Renal Pressor Substances and Nephrosclerosis[1]

Partial constriction of the renal artery, perinephritis or partial renal infarction causes hypertension. Normal kidneys contain large amounts of the enzyme renin which is pressor through its effector agent, angiotensin; acute renal ischemia elicits an immediate rise in blood pressure associated with an increased release of renin; many forms of experimental and clinical hypertension are associated with renal lesions. These observations have led to the acceptance by some of the hypothesis that the renal pressor system has a primary role in the pathogenesis of hypertension. However, repeated attempts during the last 20 years to demonstrate greater amounts of renin or angiotensin in renal vein or peripheral blood have been mostly unsuccessful or, at best, equivocal. Many explanations have been presented to account for this failure. Among them, the two extremes are: renin plays only an accessory and incidental role, if any, so that hypertension, including renal hypertension, can exist without excess circulating renin; hypertension is due to hyperfunction of the renal pressor system but the present analytical methods are too crude to detect small but crucial increases in blood renin. Whatever the merits of these arguments, the fact remains that renin is present in kidneys and possesses various activities other than pressor. Hence, one could assume that it intervenes in physiologic or pathologic situations other than hypertension, as already indicated by the recent demonstration of its participation in the regulation of aldosterone secretion[2].

Possibly because of the narrow and unfruitful approach of the past, investigations have lately become more basic and diversified in attempting to test the endocrine function of kidneys during hypertension as well as during conditions associated with salt imbalance. Three methods have been extensively used: determination of granularity of the juxtaglomerular cells, determination of pressor activity in kidney extracts, and determination of pressor activity in renal and peripheral blood. We are aware that they all

[1] Whenever used, the term renin has the same meaning as renal pressor substances and refers to a biological activity, not to a definite chemical entity.

[2] C. C. J. Carpenter, J. O. Davis, and C. R. Ayers, J. clin. Invest. *40*, 2026 (1961).

Juxtaglomerular index, renal pressor substances and nephrosclerosis during conditions associated with hypertension or sodium imbalance

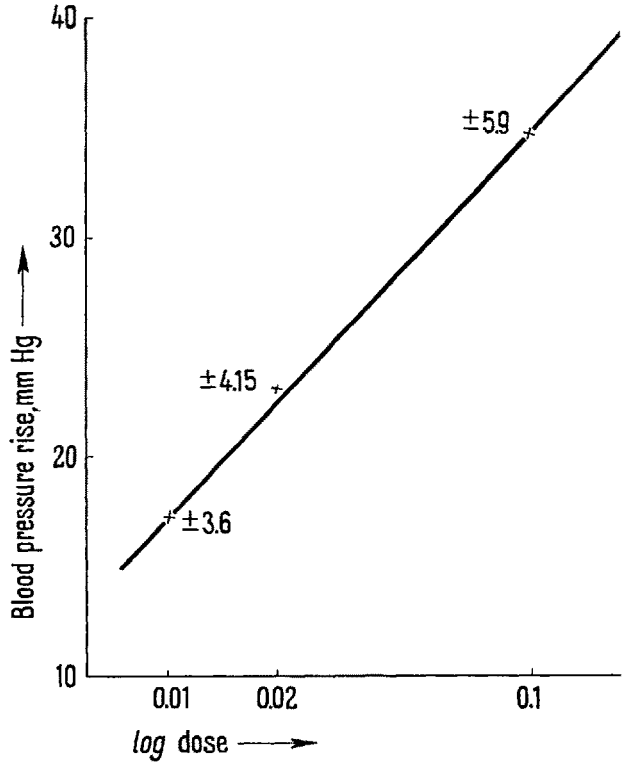
Procedure or treatment	Juxtaglomerular index in manipulated kidney	Juxtaglomerular index in contralateral kidney	Pressor Substances contained in manipulated kidney	Pressor Substances contained in contralateral kidney	Pressor Substances released from manipulated kidney	Pressor Substances released from contralateral kidney	Pressor Substances in peripheral blood	Nephrosclerosis in manipulated kidney	Nephrosclerosis in contralateral kidney
Partial renal artery constriction	++–+++ [13,15,28]	0–+ [13,15,28]	++–+++ [6,28,47]	0–+ [6,28,47]	++–+++ [9]	0–+ [9]	—	0 [48]	+ [48]
'Endocrine kidney'									
Partial infarction	0–+ [13,14]								
Figure of 8	+++ [14]	—	—	—	0–+ [8]	0–+ [8]	0 [10]	+ [13 49]	+ [49]
Encapsulation	—	—	+–++ [6]	—	0–+ [9]	0–+ [9]	0–++ [12]	+ [35]	+ [35]
DCA, aldosterone Me-androstenediol	0–+ [3,15,28]		0–+ [20,28,50–52]		0–+ [8]		0 [11]	+ [53]	
Cortisone, Cortisol	++ [29]		++ [30,54]		+–++ [54]		—	0 [55,56] ± [57]	
Post DCA hypertension	0–+ [15]		0–+ [15,58]		0–+ [8]		0 [11]	+ [57] ± [59]	
Adrenal regeneration hypertension	0–+ [15]		—		0–+ [8]		—	+ [60]	
Low Na diet Adrenalectomy	+++ [3,61]		+++ [62,63]		+++ [51]		—	0	
High sodium diet	0–+ [3,64]		0–+ [51]		0–+ [8]		—	± [61]	

have limitations and that each result has to be interpreted with reservation. However, since they test different stages in the metabolism of renal pressor substances, from their formation in kidneys to their circulation, one would expect that their combined use under similar experimental conditions would provide more information than could be obtained from a single method and would lead to useful correlations. Furthermore, the use of different criteria makes the repetition of the same error throughout these tests unlikely.

It is with this purpose in mind that we have listed in the Table changes in the juxtaglomerular index, in pressor substances contained in and released from kidneys, pressor substances in peripheral blood as well as incidence of nephrosclerosis, differentiating, when necessary, changes in the manipulated kidney from those in the contralateral untouched kidney. Before discussing these results it seems pertinent to describe briefly the testing procedures and their criteria.

Methods. The juxtaglomerular index represents a semiquantitative measure of the secretory activity of afibrillar and granular cells (JG cells) situated in the wall of the afferent arteriole near the vascular pole of the glomerulus[3]. This method is a definite improvement over previous ones which were based on purely subjective and descriptive evaluation of the degree of either development of the JG cells or their granularity[4]. Such results were purposely omitted. The JG index is calculated by grading from 0 to 4 the number and degree of granularity of the juxtaglomerular cells observed in 100 glomeruli. Normal values vary from 30 to 37 but are quite constant within each strain of rat. Although it has been postulated that renin has a juxtaglomerular origin, it is only recently that direct evidence has been presented; in dogs and rabbits, fluorescent antibodies prepared with relatively pure renin are preferentially fixed on JG cells made hyperplastic by a low sodium diet[5].

Pressor substances in kidneys are estimated from the height of the pressor response elicited in nephrectomized rats by the intravenous injection of a uniform volume of saline extracts of kidneys[6]. Pressor responses to the injection of 0.2 ml of extracts from normal kidneys at the 1/50 dilution average about 25 mm Hg in Sprague-Dawley rats. A dose response curve determined by testing various dilutions of a saline extract of normal rat kidneys shows linearity with responses between 15 and 40 mm Hg (Figure). This is in general agreement with previous observations in which a semi-purifed renin preparation of porcine origin was used as standard[7]. This method of bio-



Dose response curve obtained with a saline extract of normal kidneys tested in 24 h nephrectomized rats.

[3] P. M. HARTROFT and W. S. HARTROFT, J. exp. Med. *97*, 415 (1953).
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logical testing is not specific for renin, but from the shape of the response curve and production of tachyphylaxis on repeated injections it is probable that most, if not all, of the pressor activity is due to renin.

Pressor substances released into the renal vein blood are measured by the height of the pressor response in nephrectomized rats following grafting of kidneys on to the femoral vein and artery[8,9]. The pressure rise elicited by kidneys from normal rats averages about 20 mm Hg. For the reasons mentioned above it appears likely that this activity is due to renin.

Pressor substances in peripheral blood are estimated according to 2 methods. The first one[10] uses isovolemic cross circulation between an experimental rat and a nephrectomized partner; it permits detection of pressor activity in the blood of the experimental animal made hypertensive by infusion of angiotensin or renin, or by removal of a clamp on a completely occluded renal artery. The second method consists of incubating blood plasma with an excess of renin substrate and testing the angiotensin formed on the guinea pig ileum[11] or the toad vascular preparation[12]. This method also detects pressor activity following unclamping of a completely ischemic kidney.

Results. Results in the Table were obtained from experiments performed in rats under similar or identical conditions and are expressed in a semi-quantitative way. When an effect was noted by an author, it was graded by us according to a scale from 0 to +++; normal values were given the grade ++. This method of grading did not apply to the evaluation of nephrosclerosis. Either it was absent or present; therefore, we used only the signs 0 and +. Each number refers to the original article. Some of the surgical procedures or treatments have been grouped together on the basis of similarities in their mode of action.

It is generally assumed that renal hypertension represents a definite entity and that any change with a pathogenic connotation would be regularly found whatever the procedure used to elicit hypertension. Data in the Table tend to disprove this assumption by showing significant differences between hypertension caused by constriction of the renal artery and hypertension due to renal encapsulation and infarction. Thus, following unilateral renal artery constriction, JG index and amounts of pressor substances in kidneys and renal vein blood are normal or increased in the clipped kidney and decreased in the contralateral untouched kidney. On the other hand, in hypertension caused by unilateral lesions of the renal parenchyma, JG index and amount of pressor substances are decreased to insignificant levels in the manipulated kidney as is the secretion of pressor substances in the contralateral kidney. This apparent decrease in the pressor function of both kidneys is reflected by the absence of, or a decrease in, detectable pressor activity in peripheral blood. It is unfortunate that, as far as we know, no data are available concerning pressor activity in peripheral blood following constriction of the renal artery in rats. The different results reported for the JG index following renal infarction may be attributed to the irregular distribution of the JG cells in normal and scarred areas[13] or to the phase of hypertension at which kidneys were examined[14].

Comparison of these results with the incidence of nephrosclerosis leads to the significant observation that kidneys with a reduced pressor function are prone to nephrosclerosis while those with a normal or increased function, such as occurs in a clipped kidney, are protected against vascular disease. The association of nephrosclerosis and decreased renal pressor activity is further demonstrated during DCA, post-DCA, adrenal regeneration and salt hypertension. In all these instances, the JG index, renal content and secretion of pressor substances are low or non-existent while nephrosclerosis commonly occurs. Cortisone and Cortisol hypertension which is relatively mild and is not usually associated with nephrosclerosis does not affect the JG index nor renal content; however, secretions seem to be slightly diminished. A low sodium diet, like adrenalectomy, has the opposite effect of a high salt diet; JG cells become hyperplastic and hypergranulated and renal pressor function is stimulated.

Comments. Since the experimental conditions described above are characterized by hypertension and/or sodium imbalance, it seems appropriate to examine the role of these two factors on the renal pressor system. There is considerable evidence that renal pressor function is influenced by the level of arterial pressure to which the kidney is subjected. Thus the increase in the JG index and in pressor substances in the clipped kidney and their decrease in the contralateral untouched kidney can be attributed to the low or sub-normal pressure in the clipped kidney as compared with the high pressure in the contralateral organ. These changes in the contralateral kidney can be reversed by procedures which remit hypertension, such as removal of the clipped kidney[15] or bilateral adrenalectomy[6], or which reduce intrarenal pressure to normal levels, such as by constriction of the renal artery of the untouched kidney[15]. Furthermore, *in vitro* perfusion of kidneys under high pressure decreases the JG index[16] while low pressure, as in hemorrhagic hypotension, stimulates the release of pressor material[17]. It is still not clear whether arterial pressure[18] or pulse pressure[19] is the determining factor.

The role of sodium is best demonstrated during conditions of reduced sodium intake or increased sodium loss. A low sodium diet, like adrenalectomy, causes hyperplasia and hypergranularity of the JG cells and increases the content and release or pressor substances. The effects of sodium retention caused by a high salt diet or DCA treatment plus salt, cannot be evaluated accurately because of an associated rise in blood pressure; however, if hypertension is prevented by administration of hydralazine, renal pressor substances decrease almost to the same degree as in the control rats receiving DCA alone[20]. There is also evidence that some humoral factors of renal origin may influence renin content and secretion: a kidney contralateral to a wrapped kidney may become depleted of renin, even in the absence of hypertension[6,8]; injections of kidney extracts with little pressor activity inhibit

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secretion of renal pressor substances[21]. These are incidental or preliminary observations, the significance of which can not yet be evaluated. Also, the observation that ACTH stimulates JG cells[22] in the absence of adrenals requires further investigation since hypophysectomy has no effect[23].

Since the JG cells are the likely source of renal pressor substances, it is not surprising that they were considered as devices sensitive to pressure and sodium changes. The early concept that they were either 'Quellzellen' or contractile elements as in arteriolo-venous sphincters was soon abandoned following GOORMAGTIGH's suggestion of their endocrine nature[24]. He theorized that the granular cells of the afferent arterioles formed pressor substances acting both locally through diffusion into the arteriolar wall and systemically, and that they participated in the pathogenesis of hypertension. Furthermore, noting the close anatomical relationship between the macula densa and the JG cells, he suggested that either urine composition in the distal tubule or distension of the distal tubule may regulate the activity of the JG cells through the macula densa. Electromicroscopic observations have led to the same conclusion[25]. Histochemical studies have shown a parallelism between activity of the cells of the macula densa and the JG cells[26,27]. This anatomical and functional relationship may be related to the control of aldosterone secretion by the kidney. In this regard it may be significant that the site of action of aldosterone in the kidney is the distal tubule. More recently TOBIAN[28] proposed that the JG cells might be stretch or volume receptors. An increased stretch would be associated with degranulation and renin depletion, and a decreased stretch with hypergranulation and renin hypersecretion. Pressure would act directly while the effect of sodium would be mediated through blood volume which is decreased by a low sodium diet and increased by a high sodium diet.

The role of renal pressor substances in hypertension has been extensively discussed in recent reviews[29–31], hence we will limit ourselves to the points raised by present data. We have seen that hypertension due to partial obstruction of the renal artery is associated with normal or increased activity of the renal pressor function while hypertension caused by lesions of the renal parenchyma is associated with a decrease or absence of renal pressor substances. There is good evidence that renin participates in the first situation; a clamp on the renal artery elicits a fall in renal arterial pressure, which stimulates the JG cells and causes the release of pressor substances. Thus the subsequent rise in systemic pressure can be considered as a self-protecting and regulatory mechanism used by the clamped kidney to restore renal arterial pressure to normal levels. While this mechanism very likely contributes to the hypertensive process, by accelerating its development and increasing its severity as in malignant hypertension, one may otherwise question its significance, since it takes place only after obstruction of the renal artery. Even in that case, there is evidence that the role of renin may be limited to a period of a few days after which a secondary mechanism involving the anti-hypertensive function of the kidney takes over[32]. This so-called secondary mechanism may in reality be the primary and basic factor common to all types of renal hypertension. The various renal manipulations causing hypertension would have the common property of interfering with the antihypertensive function of the kidney. This point of view has recently been discussed by MILLIEZ[33].

Although the existence of this function seems to be well established, it is still not clear how it is exerted; the kidney may destroy a pressor principle normally present in blood or secrete an anti-pressor principle. Renoprival hypertension is a relatively slow and subtle process as compared with the almost immediate pressor effects of renal ischemia. This may explain why hypertension caused by lesions of the renal parenchyma develops more slowly than after renal artery constriction. In the latter situation, renin release would precede and later mask the early effects of a progressive failure of the anti-hypertensive function. Even if failure of the anti-hypertensive function represents the primary cause of renal hypertension, this does not imply that it is wholly responsible for it. Other factors may contribute to its maintenance. Their respective roles and their constant interplay have been described by PAGE[34] in the 'mosaic theory of hypertension'.

The relationships between hormonal and salt hypertension and the renal pressor system are better understood. It was first believed that the hypertensive effects of cortico-steroids and salt were mediated through the kidney and that renin hypersecretion resulted from nephrosclerosis acting like multiple Goldblatt clamps on the afferent arterioles. Temporal studies on the development of hypertension and of vascular disease have demonstrated that hypertension takes place before any detectable renal lesions[35]. Furthermore, we know that secretion of renal pressor substances not only ceases before hypertension[8] but also that there is no detectable pressor activity whenever nephrosclerosis is present.

The effects of cortico-steroids and salt on the renal pressor system lead us to the relationship existing between kidney and adrenals and thus to the humoral role of the kidney in the regulation of salt and water metabolism. Early studies have shown that a high salt diet, like DCA treatment, causes atrophy of the zona glomerulosa and of the JG cells while a low sodium diet has the opposite effects[36], and also that renin injections stimulate the zona glomerulosa[37]. On the assumption that the zona glomerulosa and the JG cells were the respective sites of production of DCA-like steroids and of renin, it was suggested that a functional relationship existed between kidneys and adrenals[38]. These views have been gradually confirmed by the following observations: aldosterone is formed in the zona glomerulosa[39,40] and renin in the JG cells[5]; hyperplasia of the JG cells means hypersecretion, and atrophy, lack of secretion[41]; injection of saline ex-

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tracts of kidneys or of angiotensin stimulates aldosterone secretion[2,42]; DCA or aldosterone plus salt depletes the kidneys of renin[30], and finally, the increase in aldosterone secretion secondary to acute hypotension does not take effect in bilaterally nephrectomized animals[2].

Thus, these observations support the concept that the renin-angiotensin system not only participates in the regulation of blood pressure but also is part of an homeostatic mechanism which through aldosterone regulates sodium and water balance. the sensitivity of this mechanism is such that non-pressor doses of angiotensin cause significant increases in aldosterone[2,42]. This suggests that aldosterone secretion may be used as an index of renin secretion. In view of this renin-aldosterone relationship and the association of hypertension with aldosteronism, it is therefore not surprising that aldosterone secretion was determined during renal hypertension. Recent experiments in dogs showed that aldosterone secretion remains normal during benign renal hypertension but is almost tripled during malignant hypertension[2]. Determination of the secretory rate of aldosterone in hypertensive patients gave similar results[43]. Although these observations should be extended to other types of renal hypertension, we feel that the absence of an increase in aldosterone during benign hypertension is particularly significant in suggesting that the renal pressor function was not stimulated and therefore supporting our view that the role of renin in renal hypertension is a secondary one. It should be emphasized that renal hypertension was produced by bilateral clamping of the renal artery, that dogs were definitely hypertensive with pressures between 180 and 200 mm Hg and, finally, that most of the aldosterone determinations were performed between the third and the sixth day, therefore avoiding the immediate post-clamping period when renin is released. The presence of large amounts of aldosterone in malignant hypertension elicited by severe clamping of the renal artery can be considered merely as a reflection of a continuous out-pouring of renin in an unsuccessful effort on the part of the kidney to restore renal arterial pressure to normal. Still, this does not necessarily mean that renin is the only positive factor. There is no way either to distinguish the part played by aldosterone. However, the simultaneous high levels of renin and aldosterone may be of pathogenic significance in the production of the lesions characteristic of malignant hypertension. This is supported by the observation that a situation similar to malignant hypertension can be reproduced by administration of renin or angiotensin and desoxycorticosterone to rats on a salt diet[44,45].

In this review we have attempted to summarize our present knowledge concerning the role of the renal pressor system during conditions associated with hypertension and sodium imbalance. In comparing results from methods using various criteria such as degree of development and of granularity of the juxtaglomerular cells and amounts of pressor substances in kidneys, renal vein blood and peripheral blood, we have been impressed by their concordance under various experimental conditions. In spite of their respective limitations, we feel that they are sufficiently accurate for the estimation of renal pressor function. This function is normal or increased after constriction of the renal artery and increased during sodium restriction. It is decreased during hypertension due to lesions of the renal parenchyma, DCA treatment, adrenal regeneration or salt excess. This decrease which is generally associated with nephrosclerosis, can be explained on the basis of a high arterial pressure and/or sodium retention. These observations do not support the concept that the renal pressor system is the main pathogenic factor in renal hypertension; it may, however, contribute to its development and severity. The stimulating effect of angiotensin on aldosterone secretion emphasizes the role of renin in the homeostatic regulation of salt and water and provides an explanation for the effects of sodium retention or sodium deprivation on renal pressor function. Finally, this kidney-adrenal relationship seems to be in evidence during malignant renal hypertension which is associated with hypersecretion of aldosterone and very likely of angiotensin[46].

Zusammenfassung. Eine Kritik der Methoden, die zur Bestimmung der Aktivität der renalen Pressorfunktion während Hypertension oder Natriumgleichgewicht benutzt wurden, ergibt eine gute Übereinstimmung der Ergebnisse. Es scheint eine umgekehrte Beziehung zwischen den Mengen der renalen pressorischen Substanzen in den Nieren und dem Auftreten der Nephrosklerose zu bestehen. Für die Beteiligung des Renins an der Pathogenese der benignen, renal und hormonell bedingten Hypertension besteht kein Anhaltspunkt.

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Research Division, Cleveland Clinic Foundation, Cleveland (Ohio, U.S.A.), February 8, 1962.

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