STUDIORUM PROGRESSUS

Connective Tissue Reactions in Experimentally Induced Hypertension[1]

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MEIER *et al.* have elaborated a method by which, with the aid of a foreign-body granuloma, it is possible to make a quantitative assessment of connective tissue reactivity[3]. In addition to its value for purposes of pharmacological testing[4], this method has also been used to study certain questions connected with inflammation[5] and with the influence of hormones on mesenchymal processes[6]. In view of this, it seemed interesting to investigate a systemic disease which is known to involve pathological changes in the mesenchyma such as occur in certain forms of experimentally induced hypertension, in order to determine whether such changes could be assessed quantitatively with the aid of this method and to compare the results with the pathological lesions affecting the blood vessels.

In the course of experimental hypertension, certain anatomicopathological changes take place in the blood vessels as evidence of a mesenchymal reaction. Workers engaged in research on experimental hypertension have always paid great attention to such changes, since lesions of the vessels—together with an increase in blood pressure—are the characteristic features of hypertensive disease in man[7]. Lesions of this kind, occurring in experimentally induced hypertension, were described in 1934 by GOLDBLATT, LYNCH, HANZAL, and SUMMERVILLE[8] in their first paper referring to constriction of the renal arteries as a method of provoking permanent high blood pressure. The observations made by these authors, involving the blood vessels and parenchyma of the kidney, were amplified in 1938 by CHILD[9], GOLDBLATT[10], WILSON and PICKERING[11], who studied lesions produced in other organs; they have since been confirmed by a large number of authors[12]. Typical of the changes occurring in the initial stages are patches of hyaline degeneration and necrosis of the arterioles with secondary reactions, which may lead to obliteration of the lumen and subsequent damage to the organs. These lesions affect particularly the mesostenium, pancreas, stomach, intestine, myocardium, adrenals, and brain.

The vascular lesions may vary in severity: in prolonged, slowly increasing hypertension, they consist mainly in hypertrophy of the *tunica media*; where the blood pressure rises rapidly, the degenerative processes and cellular reactions are more pronounced, presenting a complex picture reminiscent of *periarteritis nodosa*. No increase in the number of elastic fibres occurs at the start, nor any proliferation involving the *intima*—although such proliferation may later become very marked, especially where cellular reactions take place. Lesions of the kidney differ according to whether both or only one kidney is left in the organism; they involve to a varying degree the glomeruli, arterioles, arteries, and tubuli, and are accompanied by interstitial cellular reactions.

Such lesions are met with in almost all forms of experimental hypertension. It is only in so-called neurogenic hypertension, provoked either by intra-cerebral injection of kaolin or by denervation of the carotid sinus, that few, if any, arterial lesions occur[13]. According to PICKERING[14], the reason for this is probably that neither of these two forms of hypertension involves a continuously elevated blood pressure. In various species of animal, all other forms of experimental hypertension (whether of renal or extrarenal origin) give rise to anatomicopathological changes.

Lesions similar to those occurring after interventions on the kidney—except that oedema is usually more pronounced—are also observed in animals made hypertensive by an overdosage of certain steroids (e.g. cortexone[15], oestrogens, testosterone, progesterone[16], corti-

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sone[17], methyl-androstenediol[18]), by NaCl[19], by adrenal enucleation[20], by renin in combination either with cortexone and NaCl[21] or with cortisone[22], by renal damage produced with sodium-acetyl-sulphathiazole[23], by choline deficiency[24] or, finally, by prolonged treatment with large doses of vasopressin[25] and vitamin D_2[26]—to mention only a few typical examples. Generally speaking, the number and severity of the vascular lesions increases following unilateral nephrectomy.

Despite all the efforts that have been made to discover the ultimate reason for the appearance of these anatomicopathological changes, just as little is known about them today as about the causes of the rise in blood pressure. The development of the anatomicopathological lesions has been attributed to alterations in the intra- and extra-cellular concentrations of electrolytes[27], some authors suggesting that, in addition, the elevated blood pressure[28] or endogenous pressor substances such as renin[29] are also responsible. The fact that steroids which exert a marked effect on electrolyte and water metabolism are capable of causing vascular damage also appears to support the assumption that changes take place in the intra/extracellular distribution of electrolytes and water.

That high blood pressure in itself is sufficient to produce vascular lesions seems rather unlikely. As long ago as 1922, FAHR[30] postulated that, besides the increase in blood pressure, additional causative factors were evidently operative. Today, there can no longer be any doubt that—at least under experimental conditions—'neither the absolute level of the blood pressure, nor its duration is an essential factor'[31]. When the functional symptom, i.e. elevated blood pressure, is correlated with the organic lesions, it will be found, in fact, that there are animals which—despite prolonged high blood pressure—present few, if any, pathological changes. It has been suggested, however, that the occurrence of the lesions is primarily determined by the speed at which the hypertension develops[32]. But if high blood pressure were indeed to some extent responsible, there are on the other hand animals which, although subjected to the selfsame experimental intervention, do not become hypertensive and yet show vascular changes such as are typical of experimentally induced hypertension. This disparity has been noted where various different experimental methods were applied, such as clamping a renal artery[33], cellophane perinephritis[33], total nephrectomy in one of two parabiotic animals[34], or administration of NaCl in large doses[35].

Since the question whether there is an independent factor present responsible for the mesenchymal reaction had not been extensively studied in animals with renal hypertension, we conducted experiments on 136 rats, using the method of WILSON *et al.*[31] with and without contralateral nephrectomy. In addition to hypertensive animals, these rats included 59 which remained normotensive despite operation. Parallel with these experiments, we determined the mesenchymal reaction produced by a foreign-body granuloma and compared it with the anatomicopathological lesions.

In order to assess the anatomicopathological changes which occurred, the kidney, heart, mesenteric vessels, and adrenals were examined histologically [fixation in 4% Formol and Helly solution; staining with: Oil Red O, haemalaun eosin, aldehyde fuchsin (GOMORI's method) and PAS reaction (MACMANUS' method)]. The quantitative histological assessment was made without knowledge of the blood pressure levels recorded for each individual animal.

The experimental animals, weighing between 140–160 g at the onset of the experiments, were kept in metal cages at a constant air temperature of 23–25°C and a constant relative humidity of 75%, each cage containing 3 to 6 animals. They were given full-standard rat-cake (Wayne Lab-Blox Rat Diet, Allied Mills Inc., Chicago) and water *ad lib.*, but no additional NaCl. The maximum NaCl-content of this diet amounted to roughly 0·5%.

Before and after the operation, which were performed under ether anaesthesia, the systolic pressure was measured once or twice a week, using the method described by WILLIAMS *et al.*[36], the measurements being taken immediately during recovery from mild ether anaesthesia. Levels of 160 mm Hg or more were regarded as indicative of pathologically high blood pressure. Prior to the operation, the blood pressure levels varied between 100 and 130 mm Hg in the females, the average being 116 ± 9 mm Hg, and in the males between 95 and 130 mm Hg (average 112 ± 9).

In our experiments, involving several hundred female rats, hypertension developed in 25% of all animals following unilateral clamping of the renal artery, and in 53% where contralateral nephrectomy was performed as well; within 8 weeks, 10% of all animals in the former category and 21% of all in the latter had died, i.e. excluding those which failed to survive the intervention itself.

The animals examined histologically consisted not only of females (numbering 58, of which 32 were in addition nephrectomised) but also of males (78, including 32 unilaterally nephrectomised), so that possible differences attributable to sex could be taken into account. The females were killed off at the latest after 143 days, and the males after 171 days.

To determine connective tissue reactivity with the aid of a foreign-body granuloma (cotton pellets; for the method employed, see [3]) in a separate series of animals, only female rats were used at first, i.e. 218 animals upon which operations had been performed, in-

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cluding 96 which were hypertensive; for purposes of comparison, 280 normotensive controls were employed. Deviations from the corresponding normal values are shown in Figures 3, 4, and 5; these values have, in the case of each animal, been evaluated by comparison with rats of the same weight. The weight of the granuloma was determined on the 7th day following implantation; possible differences in the course of the development or regression of the granuloma were thus not taken into account. Both the fresh and dry weight of the granuloma were measured; in cases where a gain in granuloma weight was recorded, both weights were always found to increase to the same extent: hence, an increase in the weight of the granuloma is very unlikely to have been due simply to oedema of the granuloma tissue.

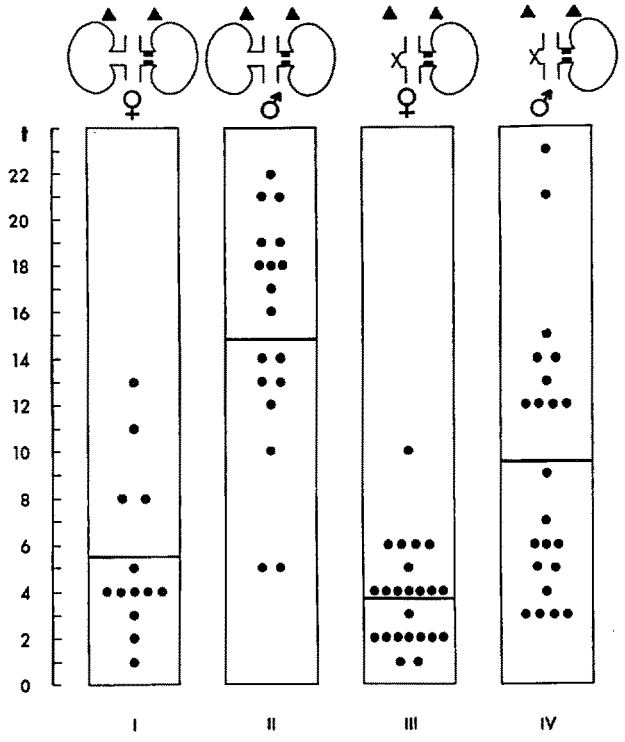

Fig. 1.—Development of hypertension in male and female rats which were examined histologically after clamping of the left renal artery, with or without contralateral nephrectomy. The ordinate shows the number of weeks elapsing before the maximum blood pressure was attained (Fig. 2). Each dot represents one animal.

Probability:		
	I/II	$p < 0{\cdot}001$
	I/III	$p < 0{\cdot}05$
	II/IV	$p > 0{\cdot}01$
	III/IV	$p < 0{\cdot}001$

Diagrams of the operative procedures based on FLOYER[37].

It has been reported that, in the case of rats, females are more susceptible to hypertension than males, especially where the hypertension is induced with cortexone[38]. Figures 1 and 2 and Table I show quite clearly that, also in the case of renal hypertension, given the same experimental conditions females attain (a) a pressure of 160 mm Hg and (b) maximum blood pressure levels much more rapidly than males; where contralateral nephrectomy is performed the onset of the rise in blood pressure and the rate at which the pressure increases is accelerated in both males and females.

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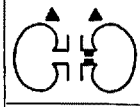
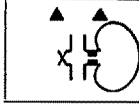
Table I

Experimental procedure	Sex	Number of weeks elapsing before pressure of 160 mm Hg attained	Average pressure in mm Hg until death	Duration of hypertension in weeks
	♀	$2{\cdot}7 \pm 1{\cdot}7$	182 ± 17	$14{\cdot}2 \pm 1{\cdot}9$
	♂	$10{\cdot}7 \pm 6{\cdot}7$	163 ± 12	$12{\cdot}4 \pm 5{\cdot}1$
	♀	$2{\cdot}4 \pm 1{\cdot}3$	188 ± 21	$6{\cdot}8 \pm 5{\cdot}4$
	♂	$8{\cdot}0 \pm 6{\cdot}2$	175 ± 12	$5{\cdot}8 \pm 4{\cdot}4$

When the lesions affecting individual hypertensive animals, whether male or female, were assessed quantitatively, it was found that the severity and incidence of the anatomicopathological damage sustained by the arteries and arterioles was not directly proportional either to the average level of the blood pressure or to the speed at which the onset of hypertension occurred; the degree of damage was also unrelated to the duration of the hypertension, which varied particularly among male rats (1–23 weeks). If, on the one hand, the males and females are examined separately and, on the other hand, those animals which have not developed hypertension are also taken into consideration, the dissociation is brought out even more clearly (Table II).

Although the hypertension in males develops more slowly and is less marked than in females, the occurrence of severe vascular sclerosis of the kidney and myocardium is far more frequent among male than among female rats. Sclerosis of this kind is also encountered in animals which have not developed hypertension. In fact, while differences attributable to sex were to be seen

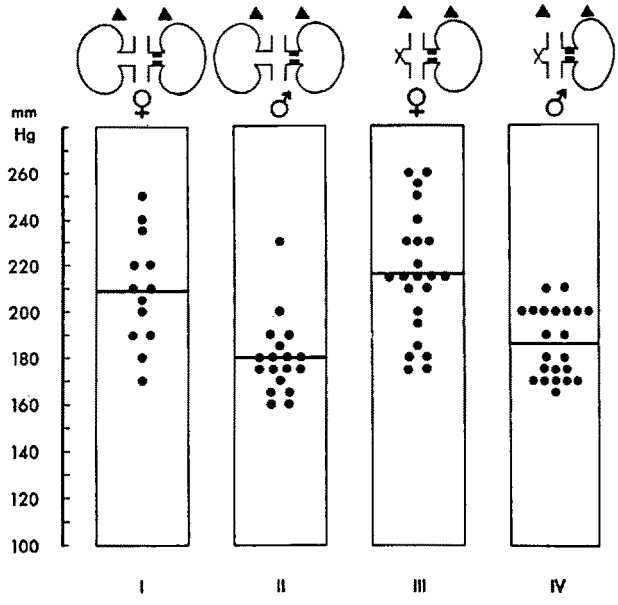
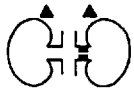


Fig. 2.—Maximum blood pressure levels (in mm Hg) of the hypertensive animals which were examined histologically. Each dot represents one animal.

Probability:		
	I/II	$p > 0{\cdot}01$
	I/III	$p > 0{\cdot}05$
	II/IV	$p > 0{\cdot}05$
	III/IV	$p > 0{\cdot}001$

Table II

Experimental procedures		Sex	Severity and incidence of extrarenal vascular lesions	Influence on granuloma weight	
				Average blood pressure		Average blood pressure
Rats with hypertension		♀ ♂	++ ++(+)	182 ± 17 163 ± 12	∅	169 ± 21
		♀ ♂	++ ++	188 ± 21 175 ± 12	+	173 ± 29
Rats not developing hypertension		♀ ♂	(+) +	128 ± 10 118 ± 8	+	111 ± 18
		♀ ♂	∅ ++	127 ± 10 128 ± 10	∅	113 ± 13

in hypertensive rats, such differences were even more pronounced in the group of animals which remained normotensive: of 9 male rats which were examined histologically 29–135 days after the left renal artery had been clamped and contralateral nephrectomy performed, 8 showed severe vascular and 3 severe renal lesions, whereas no such lesions were found in 10 similarly treated females after 65–142 days. In non-nephrectomised males (after 79–171 days) lesions, although generally less pronounced, were also evident in the majority of cases, i.e. in 20 of 27 animals (only 6 had severe renal lesions in the contralateral kidney); among 13 females (after 111–143 days) lesions were found in 7 cases, but only in 2 instances were these of moderately severe degree.

One obvious question arising at this point is that of drawing a distinction between hypertensive and non-hypertensive blood pressure. Within certain limits, at least, the choice of a 'critical' blood pressure level must to begin with remain somewhat arbitrary, particularly since—owing to the technical shortcomings of present-day methods of measuring the blood pressure—the diastolic levels, though probably of decisive importance, cannot be taken into consideration. The limit of 160 mm Hg selected by us is undoubtedly so far in excess of the margins between which the average pre-operative level ranged that animals reaching a pressure of 160 mm Hg can certainly be described as truly hypertensive. On the other hand, if elevated blood pressure is to be excluded as a possible influence on the animals which, despite operation, remained 'normotensive', then it might well be argued that the limit of 160 mm Hg is too high. The average blood pressure levels recorded in these groups of experimental animals are given in table II. This table shows that, although the average levels rose, the rise was only slight and was confined mainly to the animals which had undergone additional unilateral nephrectomy. In individual cases, however, permanent increases in blood pressure—even of a very mild nature—can certainly have had no influence, since severe vascular lesions developed in the myocardium and kidneys of male rats whose systolic pressure during the period of the experiment (lasting 94–118 days) had averaged 110 mm Hg. However, the effect of occasional brief rises in blood pressure cannot be disregarded, since a rise in pressure of this kind was, in fact, observed in two animals—although not exceeding 145 mm Hg in the one and 155 mm Hg in the other. It is thus apparent that—particularly, for example, in male rats which remain normotensive—anatomical changes occur in a large proportion of cases; hence, these cannot be caused by high blood pressure alone.

It is unlikely that—as suggested in connection with other experiments[39]—pre-existing renal damage or infections could have been responsible for the results which we obtained, since in this group of contralaterally nephrectomised rats (64 animals) no histological damage was found in the kidney extirpated at the outset of the experiment. Moreover, in our rat colony, degenerative vascular changes have not otherwise been encountered.

In the experimental procedure of WILSON and BYROM[40], the contralateral kidney appears to be important from several aspects: one particularly striking fact is that the kidney whose artery has been only slightly constricted by the clip shows few, if any, characteristic anatomicopathological changes. As a rule, such changes occur in hypertensive animals only after the contralateral kidney has been removed[38], a finding which we have been able to confirm in our own experiments. There thus seems to be a tendency for these glomerular, arteriolar, and tubular lesions to be more frequent and more clearly pronounced in females than in males, so that, in comparison with the extrarenal vascular changes, unilaterally nephrectomised rats appear to exhibit an inverse sex-dependent reaction. WILSON *et al.*[31] and BYROM[41] assume that, where the renal artery is clamped, the kidney involved is to some extent 'protected' from damage—in which case, however,

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it is difficult to understand why, following nephrectomy, lesions quickly develop in the clamped kidney. In connection with the appearance of pathological changes in the clamped kidney, it is interesting to note that SCHLOSS[42] found lesions only in those portions of the kidney which were still being supplied from collateral vessels.

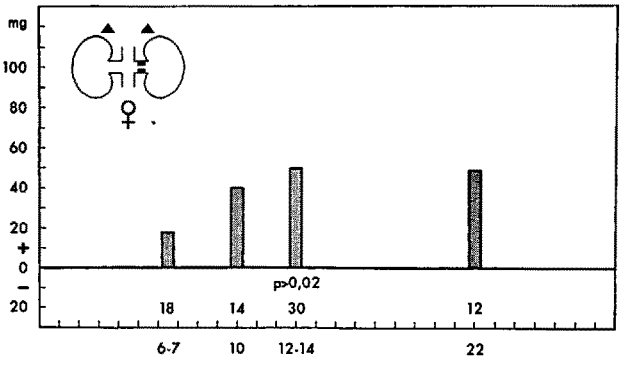

Fig. 3.—Increase in granuloma weight, as a function of duration of the experiment, in female rats which, despite clamping of the left renal artery, did not develop hypertension.
Abscissa: Duration of the experiment in weeks.
Ordinate: Difference between fresh weight of the granuloma (in mg) in experimental animals and controls. In each case, the animals were of the same weight.
Other figures: Probability (p-values) (upper row), Number of granulomas (lower row).

Under certain experimental conditions the presence of the kidneys—and of the adrenals—is not an essential prerequisite for the occurrence of pathological vascular changes; this is the conclusion reached by TURNER and GROLLMAN[28] on the basis of their experiments in which dogs with high blood pressure were kept alive for up to 40 days by means of peritoneal lavage. Despite this, however—at least in our experiments—the contralateral kidney seems to play a decisive role, in particular with regard to the appearance of lesions both in the clamped kidney as well as in the extrarenal vessels. The experiments performed show that in animals with a clamped kidney there are several factors which might be responsible for the production of vascular lesions and that some of these factors are apparently independent of the change in blood pressure. The results for the general mesenchymal reaction as revealed in the granuloma tests show a similar, though not identical, picture.

In unilaterally clamped female rats which have not developed hypertension, the weight of the granuloma rises, indicating an increased mesenchymal reaction. This phenomenon is on the one hand dependent on how long the experiment lasts, i.e. a certain latency period is necessary (Fig. 3).

On the other hand, the weight of the granuloma no longer undergoes any significant change if hypertension develops or if the kidney is extirpated. Although the histological examinations carried out on female rats which remained normotensive are not sufficiently numerous to permit of any final conclusions, the findings they yield do tally basically with the results obtained from experiments performed with the foreign-body granuloma: pathological vascular and renal lesions only appear in cases where the contralateral kidney has been retained—although, in males, lesions also develop following nephrectomy. The non-clamped, contralateral kidney must therefore be of fundamental importance, since after its removal no definite anatomicopathological vascular lesions or alterations in the foreign-body reaction can be detected in female rats which have remained normotensive.

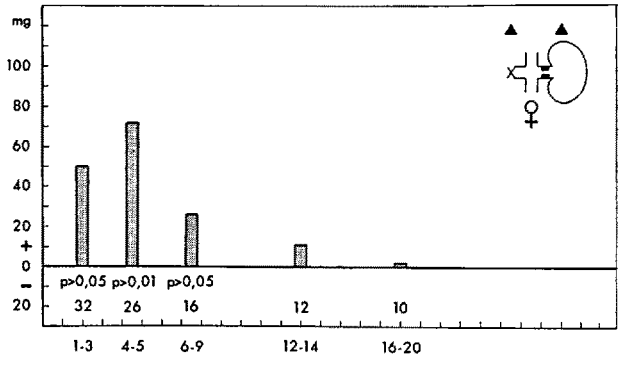

Fig. 4.—Increase in granuloma weight, as a function of speed of onset of hypertension, in female rats subjected to clamping of the left renal artery and contralateral nephrectomy.
Abscissa: Number of weeks elapsing before pressure of 160 mm Hg attained. Other figures as for Figure 3.

The situation is different in the case of animals which become hypertensive. While nephrectomy has no significant influence on the histological vascular changes, by employing the foreign-body granuloma it is possible to differentiate between the histological findings, although on the other hand this method also shows that the two phenomena of degenerative vascular lesions and altered reactions to a foreign-body stimulus do not run an identical course. In hypertensive animals, it is in fact not until the contralateral kidney has been removed that the granuloma begins to show an increase in weight—an increase which can, moreover, be correlated with the course of the hypertension, i.e. with the speed of onset and duration of the hypertension. A significant increase in the weight of the granuloma is only found in animals attaining blood-pressure levels of 160 mm Hg or more within 4–5 weeks, since in cases where the rise in pressure is more gradual the weight of the granuloma no longer deviates significantly from the norm (Fig. 4). In addition, the rats must average a pressure of at least 160 mm Hg for a minimum of 7–9 weeks (Fig. 5).

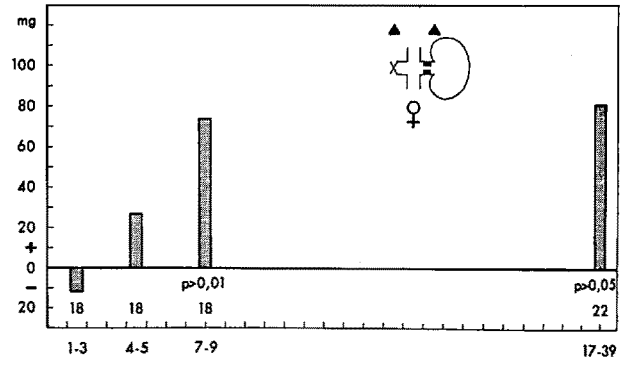

Fig. 5.—Increase in granuloma weight, as a function of duration of hypertension, in female rats subjected to clamping of the left renal artery and contralateral nephrectomy.
Abscissa: Time in weeks. Other figures as for Figure 3.

[42] G. SCHLOSS, Schweiz. Z. Path. Bakt. *11*, 109 (1948).

From this it follows, firstly, that the mesenchymal reactions and high blood pressure are not interlinked; hence, one factor responsible for the development of hypertension can be postulated and another responsible for the mesenchymal reactions. Both mechanisms are triggered off by the unilateral clamping of a renal artery. Secondly, removal of the contralateral kidney serves to promote both hypertension and pathological changes, besides which this additional intervention also produces a qualitative change in the type of hypertension affecting the animal. It can be assumed with certainty that an interplay, not merely of two, but of several elements is involved. The latter also include sex-specific elements, inasmuch as the principle or principles giving rise to the lesions are either antagonised by female or enhanced by male factors.

The mesenchymal reactions to the stimulus of a foreign-body and the degenerative vascular changes do not go hand in hand in every case—at least, where female rats are concerned—although both processes can be elicited by the same operative procedures. Differences in localisation might, among other things, have some influence in this respect; it is, in fact, already known from morphological studies that certain vascular beds, e.g. the kidneys, myocardium, and mesostenium, are particularly liable to develop lesions.

In unilaterally clamped female rats, the appearance of hypertension alters the reaction to a foreign-body inasmuch as the weight of the granuloma ceases to increase—but only if the contralateral kidney is retained. This is a fact which cannot be explained on the basis of present-day knowledge unless it be assumed that the conditions governing the growth of the granuloma are decisively modified either by the high blood pressure itself or by mechanisms—possibly of a peripheral vascular nature—which it elicits.

It is also not yet possible to say what factors may ultimately determine the change in mesenchymal reactivity. Furthermore, it is still an open question whether adrenal substances—either in a primary or only in a secondary capacity (e.g. via the parathyroid glands[43])—are responsible and whether the decisive factor is an excess or a deficiency of the regulatory principles in question.

In conclusion, it may be said that high blood pressure is not the only factor to be considered when approaching the problem of vascular damage in the syndrome of hypertensive disease. Histological studies and use of the foreign-body granuloma technique indicate a clear distinction between permanent hypertension and changes in mesenchymal reactivity, despite the fact that both symptoms can be provoked by applying the same experimental procedure. Vascular lesions such as are typical of experimental hypertension are also found in animals which have remained normotensive. The presence of high blood pressure does not necessarily go hand in hand with an increase in the severity or extent of vascular lesions. Sex-specific factors are also of importance, since females tend to show a more pronounced blood-pressure reaction, while males are more susceptible to vascular lesions, particularly of a sclerotic type. Where a renal artery is clamped, simultaneous extirpation of the contralateral kidney leads to a qualitative change in the type of hypertension involved.

[43] D. Lehr and Constance R. Martin, 20th Int. Physiol. Congr. Abstr. of communicat. Bruxelles, 555 (1956).

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Zusammenfassung

Histologische Untersuchungen verschiedener Gefässgebiete von renal hypertonischen Ratten zeigten keine Abhängigkeit der Gefäßschäden vom Verlauf des Hochdruckes. Typische Gefässveränderungen für den experimentellen Hochdruck sind auch bei solchen Tieren zu finden, deren systolischer Druck trotz Einengen einer Nierenarterie nicht signifikant anstieg. Die Bindegewebsreaktion gegenüber einem Fremdkörper wird gesteigert. Es wird unterschieden zwischen Faktoren, die für die Hochdruckentstehung, und solchen, die für eine Umstimmung des Mesenchyms verantwortlich sind. Beide Prozesse können methodisch gleichartig ausgelöst werden. Es sind sexualspezifische Unterschiede vorhanden, da im allgemeinen Weibchen zu einer verstärkten Blutdruckreaktion, Männchen dagegen zu vermehrten Gefäßschädigungen neigen, besonders zu sklerotischen Veränderungen. Bei Klammerung einer Nierenarterie führt die gleichzeitige Exstirpation der zweiten Niere zu einer Änderung des Hochdrucks in qualitativer Hinsicht.

PROPOSITA

The Validation of Soviet Claims of Vegetative Hybridization in Animals

The program of the recently held International Genetics Symposia in Tokyo included several contributions from the Soviet Union. Of outstanding interest to animal geneticists was the paper of Professor H. F. Kushner, who, together with other material, presented data which presumed to demonstrate, that by means of blood transfusions it is possible to change the hereditary constitution of animals. Thus, in one experiment, White Leghorn chickens were induced to change their plumage to a black color and almost to double their weight after four generations of transfusions of blood from Black Australorps. Similarly, turkey blood transfused into chickens led to the production of plumage patterns characteristic of turkeys. Other means of successful modifications of heredity (by transfer of albumen from eggs of one breed to those of another, parabiosis of mammals, and gonad transplants) were also described.

It is obvious that should the experiments reported be found to be repeatable with purebred material outside of the Soviet Union or its allied countries, no geneticist anywhere would be able to ignore Lysenko theories. Hence, it should be of considerable importance to the Lysenko school of thought to facilitate repetition of the work under controlled conditions by workers who could not be accused of being under any sort of pressures to obtain one type of result in preference to another.

On the other hand, Western geneticists, somewhat skeptical of the conclusions reached by Kushner (though they were presented with apparent sincerity, eagerness to convince his listeners, and with friendliness rather than belligerency) would be justified in attempting repetition of his experiments, only if they had assurance