6 to 8 h (Figure 3). In one instance however, the nuclear band formed by 3 h. The appearance of the nuclear band at 6 to 8 h agrees with the conclusion by GALLERA[3], who showed that host ectoderm differentiated into a neural plate after only 6–8 1/2 h of contact with the inductor.

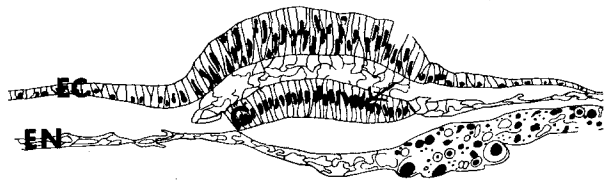

Fig. 2. Transverse section of a graft after 6 h incubation in a chick embryo host. Note the band of nuclei (arrow) in the graft ectoderm. G, graft ectoderm; EC, host ectoderm; EN, endoderm.

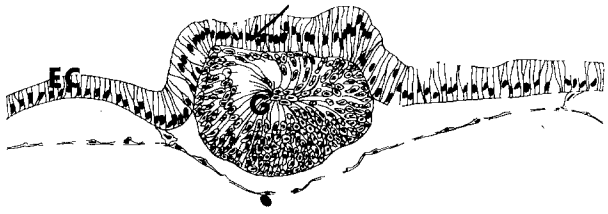

Fig. 3. Transverse section of a graft after 10 h incubation in a chick embryo host. Note the band of nuclei (arrow) in the host ectoderm. EC, host ectoderm. The graft ectoderm has formed a neural tube. G, graft neural tube.

The nuclear band in the graft ectoderm appears approximately 3 to 5 h before that in the host ectoderm. This band in the graft is comparable to the one seen in the unoperated embryo at the time of induction. Thus, it is concluded that in experimental specimens the presence of a nuclear band in graft ectoderm is an indication that the host ectoderm is being induced at this time. This suggests that primary neural induction takes place approximately 3–5 h after the graft is induced, even though the morphological results are not visible in the host ectoderm for another 3–5 h.

Résumé. L'induction primaire du système nerveux est étudiée chez l'embryon normal de poulet. Un nouveau marqueur morphologique de cette induction est découvert dans l'ectoderme. Au moment de l'induction (étape −5), une bande de noyaux apparaît dans l'ectoderme en avant du nœud de Hensen. Dans une autre série d'expériences, on a implanté un greffon de nœud de Hensen dans un autre embryon. Une bande de noyaux est aussi apparue dans l'ectoderme du greffon 3 h plus tard et dans l'ectoderme de l'hôte, 6 à 8 h après l'opération.

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Structural Basis for Resetting of Baroreceptor Regulation in Spontaneously Hypertensive Rats (SHR)

A large variety of mechanisms have been considered which may account for the high pressure level of genetic hypertensive rats[1,2]. Among these we mention hypertrophy of the vascular wall of the resistance vessels[2] and insufficiency of the sympathoinhibitory role of a noradrenergic mechanism in the brain stem[3]. These mechanisms tend to override or to diminish the baroreceptor regulatory mechanisms. However, it must be admitted that the baroreceptor reflexes still function very effectively in SHR. They have been shifted to a higher set-point of the blood pressure[4,5]. This type of functional modification can be expected if the input signal at the level of the stretch receptors has been damped. Therefore, our investigation was focused on the possibility of structural differences of the vessel wall in the stretch receptor areas of the carotid sinus and the aortic arch.

Material and methods. Spontaneously hypertensive rats of the Okamoto-strain[6] and normotensive Wistar rats of our own permanent laboratory colony established in 1956, were studied. The rats were transiently anaesthetized with ether and the femoral artery was catheterized under local anaesthesia with lidocaine. The animals were transferred in a specially designed cage[7], allowing continuous blood pressure measurement. The femoral blood pressure of the awake rats was recorded during a minimum of 30 min.

Subsequently, the animals were anaesthetized with Hypnorm® (haloanisone 10 mg/kg and fentanyl 0.1 mg/kg, s.c.). The abdominal caval vein was sectioned and the abdominal aorta was perfused retrogradely at 140 mm Hg with heparinized Ringer solution followed by 2% glutaraldehyde in 0.1 *M* cacodylate buffer (5 min). Sampling of artery segments was done at the following topographical spots: the common, internal and external carotid arteries at 2 mm from bifurcation; the aortic arch at 1 cm from the heart and the abdominal aorta 1 cm before the offspring of both external iliac arteries. These segments were post-fixed in 1.5% OsO_4 and embedded in Epon.

Transversely cut, semi-thick sections were prepared and stained using Masson's tri-chrome technique, adapted for Epon embedded tissue. Electron microscopic examination of the same material is in progress.

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First series of observations

	SHR									NCR (normotensive control rats)					
Date	26/4/71	6/5/71	25/6/71	5/4/72	24/5/72	10/7/72	11/9/72	11/9/72	11/9/72	25/6/71	25/6/71	21/6/71	24/5/72	10/7/72	10/7/72
Systolic blood pressure (mm Hg)	180				190	250	225	245					150	160	170
Diastolic blood pressure (mm Hg)	140				125	140	125	155					100	95	90
Index of intimal thickening															
Carotid arteries	+	+	+	+	+	+	+	+		−	−	−	−	−	±
Aortic arch	±	+	+				+	+	+						
Abdominal aorta				−	−	−	−	−					−	−	−

Second series: matched pair study

Age	SHR 6 weeks		12 weeks		21 weeks			30 weeks			NCR 6 weeks		12 weeks		21 weeks			30 weeks		
Date	12/2/73	12/2/73	9/1/73	9/1/73	4/12/73	4/12/73	4/12/73	17/1/73	17/1/73	17/1/73	12/2/73	12/2/73	9/1/73	9/1/73	4/12/72	4/12/72	4/12/72	17/1/73	17/1/73	17/1/73
Systolic blood pressure (mm Hg)	205	120	280	240	235	290	260	225	200	240	85	120	145	160	140	115	160	130	150	90
Diastolic blood pressure (mm Hg)	135	50	170	165	150	200	160	160	150	165	55	95	100	110	95	85	110	90	95	55
Heart rate: beats/min	440	450	420	410	400	410	400	470	390	370	390	440	440	360	450	390	480	390	420	390
Index of intimal thickening																				
Left common carotid artery	±	−	+	+	±	+	+	+	+	−	−	−	−	−	−	−	−	±	+	±
Left internal carotid artery	−	+	+	+		+	±	+	+	−	−	−	−					−	+	±
Left external carotid artery	±	−	+	±		+	+	+	+	−	−	−	−	−				+	−	−
Right common carotid artery	±	−	+	+	±	−	+	+	+	−		−	−	−	−	−	−	−	±	+
Right internal carotid artery	±	+	+	+				+	+	−		−	−	−		−		±	+	+
Right external carotid artery	−	−	+	+				±	+	−		−	−	−	−	−		+	−	±
Aortic arch	−	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	±	±	+	+
Abdominal aorta	−	−	−	−	−	±	−	±	−	−	−	−	−	−	−	−	−	−	−	−

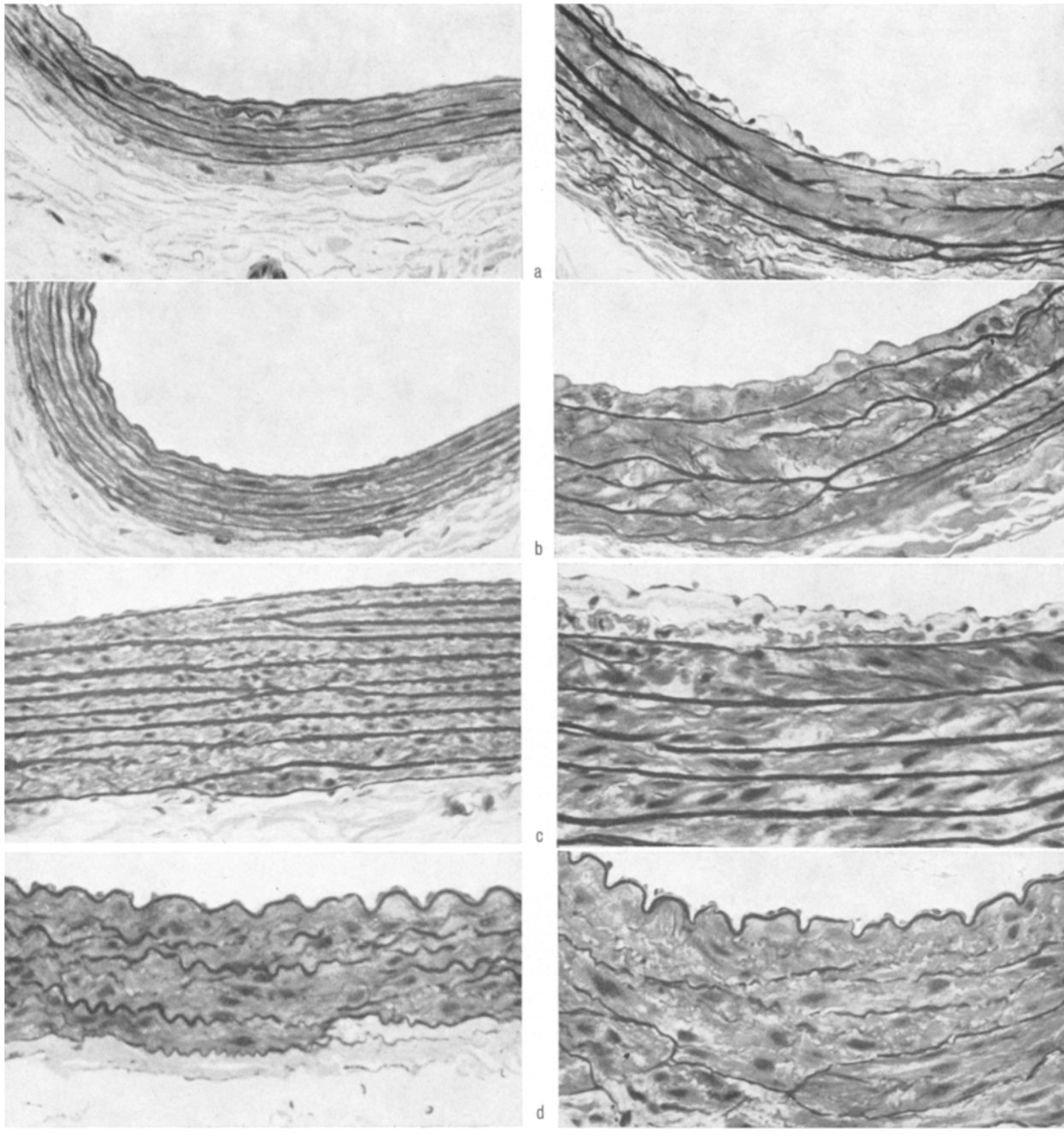
Index of intimal thickening: +, unequivocal thickening, either focal or concentric; ±, rare focal thickening; −, normal aspect of the intima. Open cases, no blood pressure was measured; the histological preparations were lacking or could not be localized with certainty.

Results. Initial observations were performed in 9 hypertensive and 6 normotensive rats. Subsequently 10 pairs of male animals, matched according to age were investigated. The results are presented in the Table and may be described as follows:

1. Blood pressure. There was a considerable hypertension in 12-to-30-week old Okamoto rats. In all the cases, hypertension was characterized by an elevation of systolic as well as of diastolic pressure. One of the younger 6-week-old rats, showed normal blood pressure.

2. Heart rate. No difference of heart rate was found between the 2 strains of rats under investigation. The mean values observed for the matched pair animals were 416 beats/min in Okamoto rats and 415 beats/min in the normotensive control rats.

3. Light microscopic observation of the vessel walls. Histological examination of the blood vessels revealed the occurrence of an intimal thickening in numerous preparations (Table). This phenomenon was never observed in the abdominal aorta, whether the rats were hypertensive or not. On the other hand, when stretch receptor areas were examined at the level of the carotid sinus or of the aortic arch, some degree of intimal thickening was already demonstrable in 6-week-old Okamoto rats.



From top to bottom: transversal sections of the internal (a) and common (b) carotid arteries; from the aortic arch (c) and the abdominal aorta (d). Left side: normotensive control rats (a and b: a 12-week-old rat; c and d: a 21-week-old rat). Right side: spontaneously hypertensive rats (matched animals). Magnification: ×300.

This intimal thickening was found in nearly all the preparations of older spontaneously hypertensive rats. This area was frequently inhabited by a variable number of cells of varying size.

On the other hand, the vessel walls of the normotensive control animals never presented intimal thickening up to the age of 21 weeks, whereas some degree of intimal swelling was present in 30-week-old rats. This subendothelial proliferation was either concentric or restricted to one or more focal areas. These observations are illustrated in the Figure. Furthermore, the distance between the elastic laminae of the media was generally larger and relative hypertrophy of the smooth muscle occurred in the blood vessels of SHR. These differences were found in the abdominal aorta as well as in the other vascular preparations.

Discussion. Our observations concerning the blood pressure level in SHR are in agreement with the finding that the recent generations of this strain develop hypertension within the first 7 weeks of life[8]. This high blood pressure level is not accompanied by relative bradycardia, which provides an additional indication that the baroreceptor regulation has been shifted towards a set-point of higher blood pressure values. The histological findings demonstrate an intimal thickening in vessel walls of spontaneously hypertensive rats, more particularly in the region of the carotid sinus and of the aortic arch, where stretch receptors are located at the margin between the media and the adventitia of the vessel walls[9]. Medial hypertrophy was generally found in SHR irrespective of the topographical origin of the blood vessel. Similar modifications have been described in rats after induction of DOCA-hypertension[10].

According to REMINGTON[11] the arterial wall may be considered as an inner, distensible coat (the media-intima layer) covered by an outer restricting jacket (the adventitia).

The thickening of the inner coat may constitute a damping factor for the transmission of the intravascular pressure pulse through the vessel wall towards the stretch receptor endings. The mechanical properties of the intimal and medial structures apparently differ widely. Since techniques are not yet available for measuring the distribution of mechanical strains across the vascular wall thickness[12], the extent of baroreceptor resetting due to intimal swelling and/or medial hypertrophy will be difficult to evaluate.

In any case, a damping of the pressure pulse signal resulting from this vascular thickening could precisely lead to the type of baroreceptor resetting which has been described[4,5]. Whether these histological modifications of the vascular wall in the stretch receptor areas of SHR play a causative role or are merely a consequence of the high blood pressure, cannot be settled at present. They certainly constitute another loop in the vicious circle of spontaneous hypertension[13].

Zusammenfassung. Nachweis, dass in Ratten mit genetischem Hochdruck und normalem Herzrhythmus Verdickungen des Endotheliums im Karotissinus und im Aortabogen beobachtet werden. Eine Hypertrophie der Gefässmuskulatur war nachweisbar, was zu einer Abschwächung des Drucksignals zur Stelle der Pressorezeptoren führte. Diese dürften teilweise verantwortlich sein für die Verschiebung der Pressorezeptor-Steuerung bei genetisch hypertensiven Ratten.

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The Inhibitory Effect of α-2-Macroglobulin on Tumour Growth

In a previous description of the detoxification effect exerted by α_2-globulin during massive tumour lysis[1], an interesting side effect was noted in a few of the tumour-bearing rats. Remnants of tumour cell aggregates, which normally supported a restoration of the original tumour mass within a 10-day-period, exhibited a much reduced mitotic activity, so that an interval of about 18–23 days elapsed before the tumour became palpable again. Testing various identifiable subfractions of the α_2-globulins revealed that only the α_2-macroglobulin exhibited a major delaying action on tumour growth. As yet the only identifiable biochemical property of α_2-macroglobulin is its binding to, and its potent inhibitory effect on various proteolytic enzymes[2–4].

Material and methods. Leukaemia cells (L 1210) and the DÄNA-435 tumour of the R-rat (Berlin-Buch) have been used. The reason behind the choice for these model systems was that leukaemia cells produce proteases essential for cell division[5], while the DÄNA-435 tumour is an immunologically well-controlled tumour. The α_2-macroglobulin (α_2-M) was prepared from rat serum as described by previous authors[6–8]. The serum was initially fractionated on a DEAE column. The α_2-M fraction was concentrated by dialysis through PM-30 Diaflo membranes followed by equilibration on Sephadex G-100. The purity of the α_2-M fraction was checked by immunoelectrophoresis with the aid of specific anti-serum[9]. Using standard enzyme essays[3,4] it could be shown that

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