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Microinfarction as a result of hypertension in a primate model of cerebrovascular disease

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Abstract Ten adult cynomolgus monkeys were studied as a non-human primate model of hypertensive cerebrovascular disease. Seven were made hypertensive by surgical coarctation of the aorta and three served as unoperated controls. After survival periods of 8–30 months, the brains were serially sectioned and surveyed for neuropathological changes. The most conspicuous change was minute areas of microinfarction in the white and gray matter. The lesions were of irregular shape with an average maximum diameter of less than 0.5 mm. They were slightly larger in the gray than in the white matter and appeared to be of different ages. Their area of predilection was the white matter of the forebrain, with smaller numbers in the cerebral cortex and scattered lesions elsewhere in the forebrain, brain stem and cerebellum. These microinfarcts did not correspond to usually described lesions in the human brain in hypertension or in other animal models of hypertensive cerebrovascular disease. We suggest that they represent an early change in the natural history of hypertensive neuropathology.

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Introduction

Arterial hypertension, a condition that affects over 25% of the adult population of the United States [31], has been identified as a major risk factor for cerebrovascular disease [12, 18, 21, 29, 30, 34, 48]. Cerebrovascular disease in humans produces a variety of cognitive impairments ranging from focal dysfunction to dementia [9]. In addition to these dramatic effects of hypertension, there is also evidence for a more subtle, progressive decline in memory, executive function, and attention [5, 13–15, 19, 35, 43, 49, 53–55]. The neuropathological substrate for these subtle declines is unknown.

In our non-human primate model of hypertension, using coarctation of the aorta, we have noted a similar progressive decline in cognitive function [36, 37]. The present study was performed in parallel with those clinical studies to provide a catalogue of the changes encountered in the hypertensive monkeys. Since only a few of these monkeys were clinically tested, it is not yet possible to determine the relationship of the observed changes to intellectual decline.

The predominant change that we have identified is a microinfarct, a lesion much smaller than that generally attributed to chronic human hypertension. Other pathological changes, such as leuko-araiosis [51], Binswanger's subcortical leukoencephalopathy [3, 17, 41, 46], lacunar infarction [16], and hypertensive encephalopathy [8, 47] were not identified.

Materials and methods

The procedures used in the studies described in this manuscript have been fully approved by he Boston University School of Medicine Institutional Animal Care and Use Committee (IACUC). Ten wild-caught, adult male cynomolgus monkeys (*Macaca fascicularis*) of

Philippine origin were used. Of these, seven were made hypertensive and three were used as normal controls. All monkeys were housed in the AAALAC-approved Laboratory of Animal Science Center at Boston University Medical Center and were maintained on Purina monkey chow for 6 months before entry into the study. Hypertension was produced by surgically coarcting the aorta, details of which have been previously described [26]. Briefly, a 1-cm segment of thoracic aorta, at a level just below the hilum of the left lung, was narrowed to a luminal diameter of 2.0–2.5 mm using surgical callipers and a Casteneda partial occlusion vascular clamp (Pilling Instruments, Fort Washington, Pa.). A supporting band of umbilical tape was then drawn around the coarcted segment and sutured without further constriction of the vessel. The coarctation of the aorta resulted in a decrease in luminal area of about 75–80%, as indicated by autopsy findings. During the immediate 3-week post-operative period, the monkeys were given angiotensin I converting enzyme inhibitors, diuretics and digoxin to prevent heart failure. All drugs were then discontinued.

During the base line period, and at 2- to 3-month intervals throughout the experimental period, measurements were made of body weight, plasma cholesterol [1], triglycerides [52] and high density lipoprotein (HDL) cholesterol [25]. Routine blood analyses also were performed with an autoanalyzer and included sodium, potassium, glucose, blood urea nitrogen, creatinine, and calcium. Collection of venous blood for chemical analysis and measurement of blood pressure were made under sedation with ketamine-HCl (10 mg/kg i.m.) following an 18- to 24-h fast.

For measurement of HDL cholesterol, fasting blood specimens were collected in tubes containing disodium ethylenediamine tetraacetic acid (1 mg/ml). HDL cholesterol was isolated at a density of 1.210–1.063 g/ml by differential density ultracentrifugation following which the cholesterol contained in this fraction was measured [28].

The blood pressure in the brachial artery was monitored indirectly by the ultrasonic cuff method weekly in the post-operative period and then at intervals of 2 months with the use of the Arteriosonde [27]. Direct measurements of the intra-arterial pressure in the brachial and femoral arteries also were performed on the day of the surgical coarctation, at 3 and 12 months after the surgery and at the time of sacrifice. After exposing and cannulating the brachial and femoral arteries, the arterial pressure in these arteries were simultaneously measured with strain gauge transducers attached to a Beckman dynograph recorder. Direct measurements of brachial arterial pressure tended to be higher than the indirect measurements. Both of these were used to assess changes in blood pressure.

At the completion of the study, the monkeys were sedated with ketamine and administered an overdose of sodium pentobarbital. They were perfused transcardially with neutral buffered formalin. The brains were removed and stored in 10% neutral buffered formalin and embedded in celloidin. The brain was serially sectioned at a thickness of 35 μm with each 20th section stained with Nissl stain and the next two adjacent sections stained, respectively, with the Loyez myelin stain and with hematoxylin and eosin (H&E). All stained sections in the whole brain serial section were surveyed

Table 1 Clinical data (*coarct.* coarctation, *HDL* high density lipoprotein, *NA* not available)

	Controls			Hypertensive group						
Monkey no.	822	827	879	842	844[a]	860	861	869	879	875
Duration of coarct. (months)	–	–	–	11	11	8	9	29	30	18
Blood pressure (mmHg)[b]										
Systolic	118	104	105	218	185	192	200	240	210	207
Diastolic	68	72	67	142	128	135	122	116	109	113
Plasma lipids (mg/100 ml)[c]										
Cholesterol	127	122	107	135	83	130	122	120	150	139
HDL cholesterol	67	68	70	53	34	63	43	53	51	39
Triglycerides	37	40	39	40	49	38	40	51	53	47
Heart weight (g)	15	19	22	49	43	30	39	44	57	NA
Heart/body weight (g/kg)	3.1	3.5	3.8	7.4	7.2	5.5	8.0	6.4	7.7	NA
Brain weight (g)	62	72	65	66	70	66	76	NA	NA	NA

[a] Died during course of study
[b] Average brachial arterial pressure
[c] Average levels

Table 2 Microinfarct distribution (*WM Str. Border* border between the striatum and the white matter)

Monkey no.	842	844	860	861	869	870	875
Hemispheric WM	69	4			1	7	
Internal capsule		1	5	25	3		
External capsule	1			1			
Extreme capsule							
Cerebral cortex	1	1	1	4			
Claustrum					1	1	
WM Str. Border							
Striatum	1						
Globus pallidus	1						
Amygdala							
Thalamus							
Cerebellar WM							
Anterior com.							
Hippocampus		1					
Others	2[a]			1[b]			
Total	75	7	6	32	4	7	0

[a] One lesion each in optic tract and mesencephalon
[b] Single lesion in the nucleus raphe dorsalis

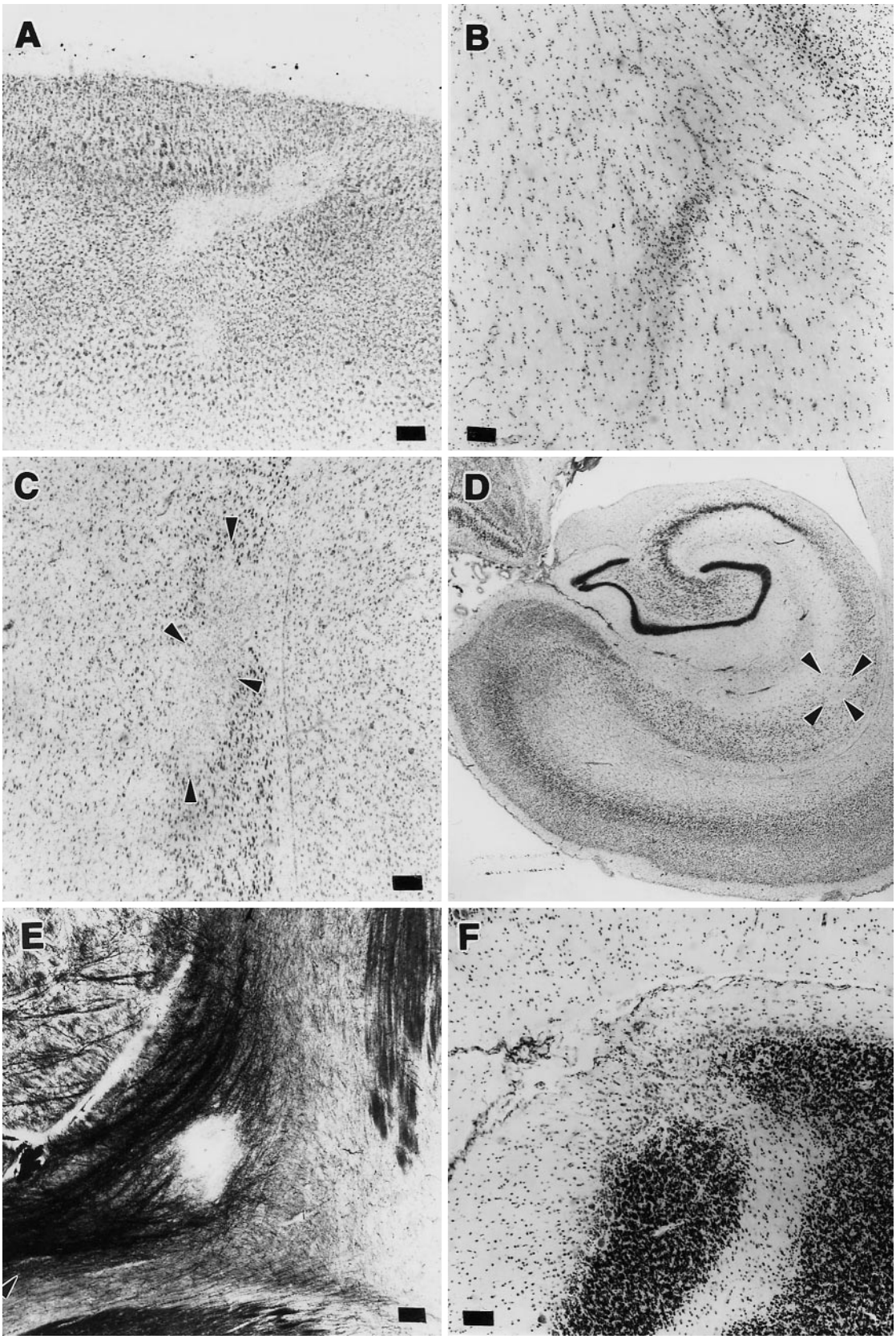

Fig. 1 Examples of microinfarcts in the cerebral cortex (**A**), in the subcortical white matter (**B**), in the claustrum (**C**, *arrowheads*), in the field CA1 of the hippocampus (**D**, *arrowheads*), in the ansa lenticularis (**E**), and in the cerebellar cortex (**F**). Note the total loss of neurons within the gray matter lesions (**A**, **C**, **D**, and **F**) and of myelin in the white matter lesions in **E**. **A**–**D**, **F** Nissl-staining; **E** Loyez myelin staining. *Bars* **A**–**C**, **E**, **F** 100 μm

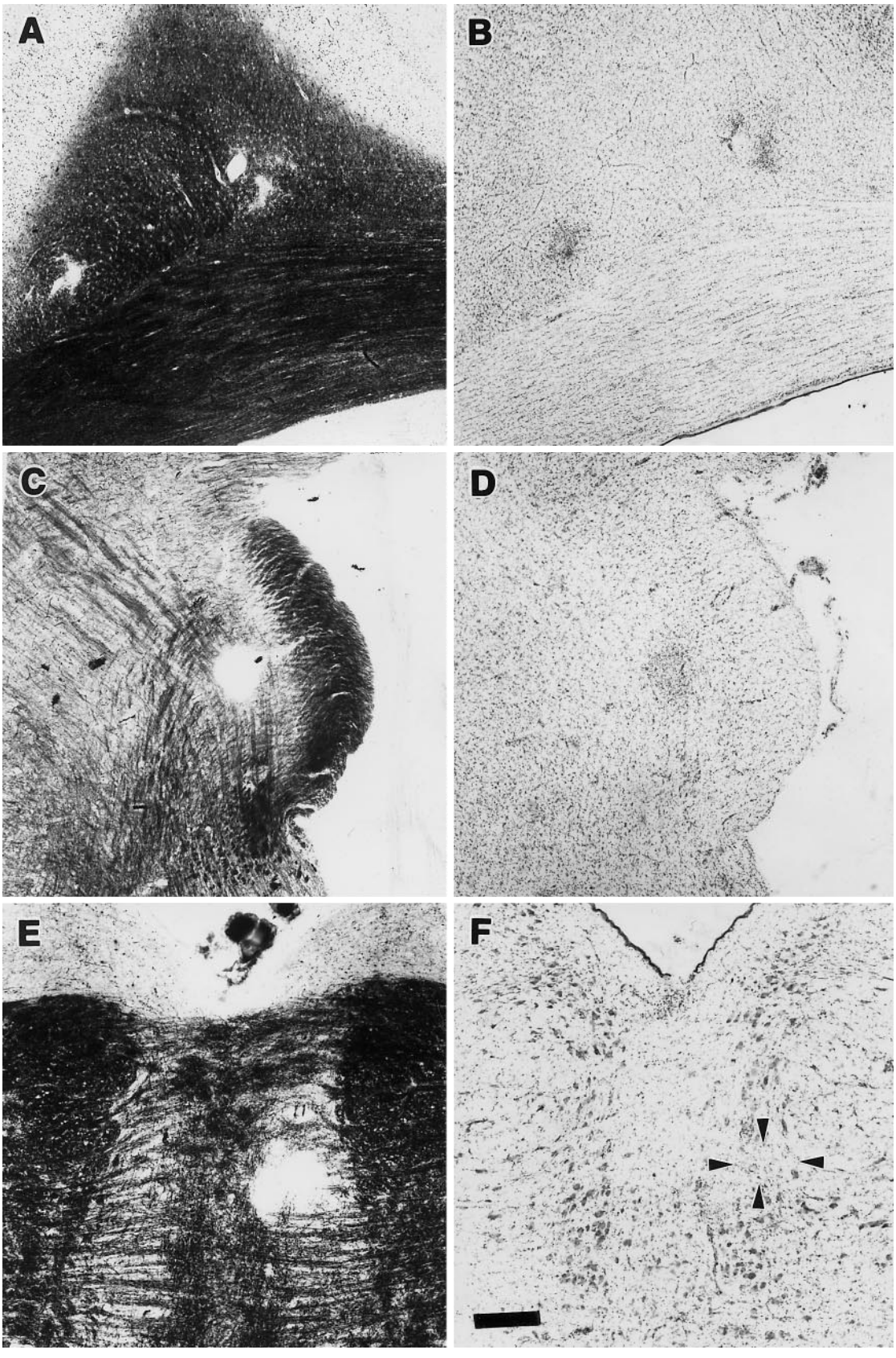

Fig. 2 A–F Microinfarcts in adjacent Nissl- and myelin-stained sections. Three lesions in the subcortical white matter in the cingulate gyrus are shown in **A** and **B**, in the gray matter just deep the brachium of the inferior colliculus in **C** and **D**, and in the nucleus raphe dorsalis in **E** and **F** (*arrowheads*). Note the total loss of myelin in these lesions. **A**, **C**, **E** Loyez myelin staining; **B**, **D**, **F** Nissl staining. *Bar* 200 μm

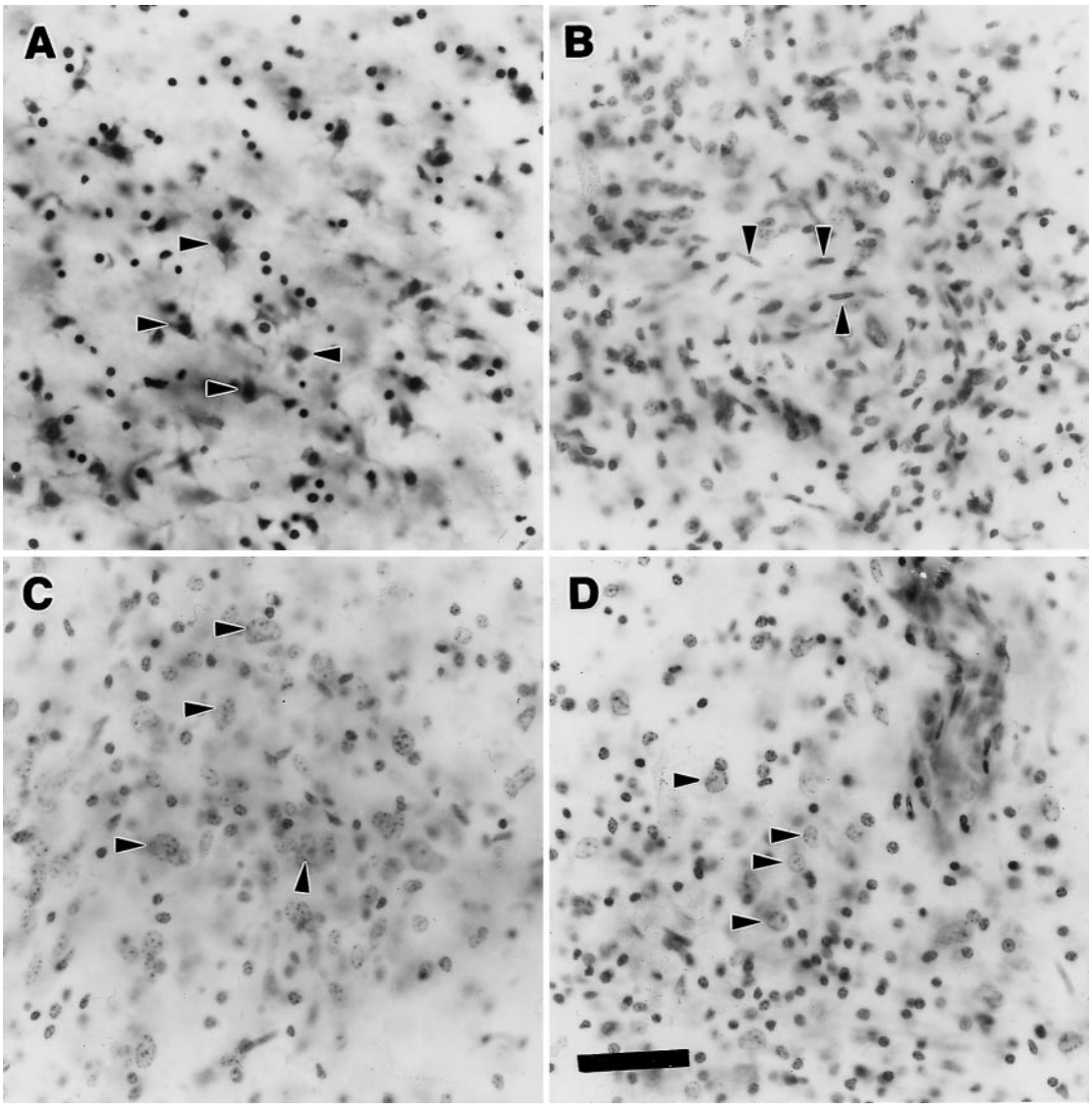

Fig. 3 A–D High-power photomicrographs to show different stages of evolution of the microinfarcts. In **A** a recent infarct with universal ischemic nerve cell change (*arrowheads*) can be seen. A slightly older lesion with numerous reactive microglial cells (*arrowheads*) is shown in **B**. An older lesion with marked hypertrophy of astroglial cell nuclei (*arrowheads*) is shown in **C**. In **D** a microinfarct is closely associated with a hyperplastic blood vessel. It shows a more quiescent glial scar with few mildly hypertrophic glial cell nuclei (*arrowheads*). Nissl stain. *Bar* 50 μm

with a stereomicroscope and the pathological changes noted confirmed with a compound microscope. The entire brain was available from hypertensive monkeys 842, 844, 860, and 861 and one half of the brain, including one half of the brains stem, from hypertensive monkeys 869, 870, and 875. The entire brain was available for the three controls.

Results

Clinical findings

Clinical data for the three control monkeys and the seven hypertensive monkeys are shown in Table 1. The average systolic blood pressure ranged from 185 to 240 mmHg with the average diastolic blood pressure varying from 109 to 142 mmHg. Heart weight was available for six of the hypertensive monkey. These all developed myocardial hypertrophy, with heart-weight to body-weight ratios that ranged from 5.5 to 8.0 g/kg (mean = 7.0 g/kg) as compared to a range of 3.1–3.8 g/kg in the control group. At necropsy, one of the hypertensive monkeys (no. 860) showed evidence of cardiac failure and three (nos. 842, 844, 860) developed retinopathy with hemorrhages and exudates. The serum cholesterol, triglycerides, and HDL cholesterol in the hypertensive group showed no change from control values. The blood electrolytes, BUN, creatinine and glucose also showed no significant changes and were comparable to the values observed in the controls.

Table 3 Incidental findings. For mineral deposits the maximum deposit noted was graded +++, and those areas without demonstrable deposits *0* (*tr* trace)

	Controls			Hypertensive group						
Monkey no.	822	827	879	842	844	860	861	869	870	875
Cerebral cortex	+	+	tr	0	+	+	tr	+	0	0
Striatum	++	++	++	+	+	++	++	+	+	tr
Globus pallidus	++	+++	+++	+++	++	++	++	+++	++	tr
N. basalis	++	++	+++	+	++	++	+	++	0	+
Amygdala	+	tr	0	tr	tr	0	tr	+	0	0
Thalamus	+	+	+	+	tr	+	+	tr	+	tr
Cerebellar nucl.	0	+	+	0	tr	0	0	0	0	0
Subst. nigra	++	++	++	++	++	tr	++	–	tr	0

Table 4 Perivascular macrophages: the numbers are the number of vessels with perivascular macrophages noted throughout the serial sections with a stereomicroscope

	Controls			Hypertensive group						
Monkey no.	822	827	879	842	844	860	861	869	870	875
Hemispheric WM	15	59	8	14	4	14	24	1	1	2
Internal capsule		9	4	1	1				1	
External capsule	1	1		2	1				1	
Extreme capsule	4	7		3	1	4	7			
Cerebral cortex		2			2	2				
Claustrum			1							
WM Str. Bord.			13	1		1				
Striatum	2	1	3	1	1	5	3			1
Globus pallidus			1		1					
Amygdala			5				3			
Thalamus		1	1					3	1	1
Cerebellar WM		2								
Anterior com.			3		1	4				
Hippocampus						1	4			
Totals	22	82	39	22	12	31	38	4	3	4

Neuropathological findings

The most conspicuous finding in the brain of hypertensive monkeys was minute areas of infarction. These were not found in controls. Their distribution according to anatomical location is shown in Table 2 with examples of these lesions shown in Figs. 1–3. These microinfarcts measured (415 ± 230) × (225 ± 125) μm (mean ± SD of the greatest measurement and a measure perpendicular to this measurement, $n = 129$). They were smaller in the white matter [(400 ± 220) × (210 ± 120) μm, $n = 114$] than in the gray matter [(505 ± 285) × (295 ± 165) μm, $n = 15$]. The differences in size between the lesions in the white and gray matter were not statistically different. Their areas of predilection was the white matter of the forebrain, particularly the capsular system and the hemispheric white matter of the corona radiata and centrum semiovale. They were infrequent in the periventricular white matter. The next highest density was in the cerebral cortex, with the remainder scattered throughout the forebrain, brain stem, and cerebellum. They often contained a centrally placed, prominent blood vessel and the blood vessels in the surrounding area were often conspicuous with thick vessel walls (Fig. 3D). In the gray matter, the microinfarcts were sharply circumscribed with no surviving neurons within them. Most of the 15 gray matter lesions were old with a quiescent glial scar. Some were more recent with 3 showing a marked degree of glial cell nuclear hypertrophy and hyperplasia, 1 with microglial cells (Fig. 3B), 4 with macrophages, and 2 with ischemic nerve cell change (Fig. 3A). The 114 white matter lesions were also of different ages. Twenty-two showed a quiescent glial scar (Fig. 3D), the remainder showing a variable degree of glial cell nuclear hypertrophy (Fig. 3C). Ten lesions showed microglial cells and 13 contained macrophages, most of which had gold to brown pigment. In none of these gray or white matter lesions were polymorphonuclear leukocytes identified. Many of the white matter lesions appeared to be areas of incomplete infarction, with astroglial cells intermixed with oligodendroglial cells. However, myelin-stained sections, adjacent to the Nissl- or H&E-stained sections, generally showed complete loss of myelin (Fig. 2A–F).

In none of the hypertensive monkeys was there evidence of segmental arterial necrosis, microaneurysm formation or frank hemorrhage. None of the animals developed atherosclerosis. Myelin pallor, when present, was closely related to white matter microinfarction.

Another finding in these monkeys was the presence of mineral deposits in various locations within the brain and the occurrence of perivascular mononuclear cells scattered

throughout the brain. Quantitative and semiquantitative documentation of these changes in the seven hypertensive monkeys and the three controls (Tables 3, 4) suggests that these findings were incidental findings unrelated to hypertension.

Discussion

The most conspicuous finding of the present study was the presence of minute areas of infarction in each of the hypertensive monkeys. None were found in any of the normal controls. Most of the lesions appeared to be old, while other showed evidence of having been recently formed.

The microinfarcts were irregularly shaped and of relatively uniform size with an average maximum diameter of slightly less than 0.5 mm. In the gray matter these lesions were characterized by a total loss of neurons and in the white matter by marked loss of myelinated fibers. The microinfarcts appeared with greater frequency in the white matter of the forebrain, particularly in the capsular system and the hemispheric white matter of the corona radiata and centrum semiovale. The area with the next highest density was in the cerebral cortex, with the remainder scattered throughout the forebrain, brain stem, and cerebellum.

With respect to individual monkeys, the largest number of microinfarcts occurred in monkeys 842 and 861. Of interest, monkey 861 had the highest heart weight/body weight ratio and monkey 842 had the third highest heart weight/body weight ratio and the highest maximum diastolic blood pressure. These observations suggest a close relationship between these indices of the severity of hypertension and the number of microinfarcts.

The relationship of the microinfarcts observed in this primate model to the classically described focal lesions in chronic hypertension in the human brain is uncertain. The lesions are smaller than lacunar infarcts, which according to Fisher [16] measure 0.5–15 mm in diameter. They also differ from lacunar infarction in that they are not associated with obvious segmental degenerative changes in penetrating arteries or vascular occlusions, conspicuous changes in the brains with lacunar infarction [10, 16].

In contrast, the size of the microinfarcts is similar to that reported in hypertensive encephalopathy. However, the appearance of the lesions, the associated vascular changes, and the distribution pattern of the lesions is different. In human hypertensive encephalopathy, Chester et al. [8] reported that arteries in the brain and retina show segmental fibrinoid necrosis with thromboses of arterioles and capillaries. These vascular changes are associated with petechial hemorrhages and microscopic or miliary infarction. The latter measure from approximately 100 μm to 1–2 mm in diameter. These lesions in man show preferential localization in the basis pontis, followed by the basal ganglia, cerebral white matter, cerebral cortex, and spinal cord.

The distribution pattern and morphology of the microinfarcts in the hypertensive monkeys also differ form that found in rat models of acute, severe hypertension and in rat models of severe established hypertension. In these models the lesions occur predominately in the cerebral cortex in the location of the arterial border zones and to a lesser extent in the thalamus [11, 38, 44]. The characteristic lesions are microinfarcts with rarefaction of the neuropil and preserved neurons, cyst formation, and occasional hemorrhage [39, 40, 44]. Ogata et al. [39] felt that these lesions were due to brain edema and, in a serial section study of five stroke-prone, spontaneously hypertensive rats, Ogata et al. [40] noted that they were related to single or multiple arterial occlusions. These arteries, like those noted in man by Chester et al. [8], showed fibrinoid degeneration. Thus, not only is the distribution of the infarcts different than that found in man and in animal models of severe hypertension, there are differences in the details of the pathology and associated vascular changes.

The microinfarcts observed in the hypertensive monkeys also do not appear to be related to leuko-araiosis. This term, originally coined by Hachinski [24], denotes a hypodensity in the white matter beneath the lateral ventricles in computed tomography scans or intense white matter signal in this location with magnetic resonance imaging (MRI). Leuko-araiosis appears to be related to both age and hypertension [20, 50, 51]. In a postmortem MRI study, van Swieten et al. [51] noted this change in a moderate to severe degree in 10% of the brains from individuals between 60 and 69 years of age and in 50% of brains from individual between 80 and 89 years of age. The MRI appearance of periventricular change correlated well with histological evidence of loss of myelinated fibers, gliosis, and abnormally thick arterioles measuring up to 150 μm in diameter. In some cases there were small white matter infarcts. The monkeys lack both the periventricular loss of myelin and the vascular changes noted by van Swieten et al. [51].

A further consideration is the relationship of these lesions to Binswanger's subcortical leukoencephalopathy, a disease originally described by Binswanger in 1894 and later called Binswanger's disease by Alzheimer [2]. It has received extensive attention in the literature [3, 6, 7, 17, 41, 42, 46]. The hallmark of Binswanger's disease is a dementia that occurs in association with the loss of subcortical myelin that is greater in the subventricular zone, sparing of the subcortical myelinated U fibers, and severe disease of the medullary arteries that supply the affected region. The vast majority of individuals, but not all, have systemic hypertension [3, 32, 33, 46]. Fisher [17] in his review, describes scattered foci of white matter destruction" ...from typical lacunar infarcts 3–6 mm in diameter at one end of the spectrum, down to merely spongy looseness of the tissue without frank necrosis". In two cases personally observed by Fisher [17], serial sections failed to reveal evidence of vascular occlusions. Lacunar infarction occurs in 87% of the cases [17], indicating a close relationship of this change to Binswanger's disease. This relationship has prompted Román [45] to propose the term "lacunar dementia" to encompass both. The lesions in the hypertensive monkeys are smaller than those noted in Binswanger's encephalopathy and there is no evidence of diffuse white matter loss, subventricular accentuation of

the lesions, or severe disease of penetrating arteries. Further, unlike in Binswanger's disease, the lesions are scattered throughout both white and gray matter rather.

The microinfarcts observed in the present study resemble those reported by Garcia et al. [22]. These authors studied five hypertensive monkeys with coarctations of the aorta of 2-month to 2-year duration. They noted grossly visible 'spongy' lesions and selected these for detailed electron microscopic study. These measured 0.5 mm in diameter, were present in all five monkeys in a random pattern, and were most abundant at 2 years after the coarctation. In these areas, the capillaries were dilated with flattened endothelium, interrupted endothelial linings, increased thickness and deformity of the basement membrane, and deposition of collagen and osmiophilic material. In comparable lesions in the human brain, they noted, in addition, deposition of fibrin. They stated that the lesions resembled areas of brain ischemia with reperfusion, and suggested possible" ...successive episodes of regional ischemia and/or hyperperfusion." Garcia et al. [23] later noted that this change was most marked in the striatum and occurred in relationship to increased arteriolar wall to lumen ratios. This predilection for the striatum was not noted in our material.

A final possibility is that the microinfarcts are embolic in origin. Against this possibility is the lack of evidence of hemorrhage in any of the lesions, the lack of evidence of emboli elsewhere in the body, either clinically or at the time of autopsy, and the absence of a source of emboli in the general autopsy.

In summary, we report the occurrence of multiple microinfarcts in the brain of hypertensive monkeys that occur in both the white and gray matter. Their relatively uniform size suggests that they are due to ischemia in the territory of a particular caliber of blood vessel. They occurred in relationship to hypertrophic arteries that show no evidence of more advanced hypertensive cerebrovascular disease such as occlusion or segmental pathology, suggesting that they may be an early change in natural history of hypertensive neuropathology. It is possible that these microinfarcts may have been missed or overlooked in routine autopsy sections taken from hypertensive individuals. In the hypertensive monkey these lesions were present in relatively small numbers and were identified in a meticulous search of a large number of whole serial sections. In consort with behavioral testing, which shows evidence of a progressive decline in cognitive function [36, 37], the microinfarcts appear to be developing up to the time the animal is killed.

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