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Effects of Radiation on the Hypothalamus in Monkeys

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In 1954, Arnold published a paper on the effects of X-radiation on the hypothalamus of 6 monkeys, and in that same year he together with Percival Bailey and their associates dealt with the changes occurring in the brain in general in 40 monkeys (Arnold; Arnold and Bailey; Arnold, Bailey and Harvey; Arnold, Bailey, Harvey *et al.*; Arnold, Bailey and Laughlin). Their monkeys (*Macaca mulatta*) were adults of both sexes. Under Nembutal anesthesia, they were exposed transtemporally or transrostrocaudally to beams of 23-MeV X-rays. These beams were 1.0 and 2.5 cm in diameter, respectively, and the corresponding dose rates were 150 R/min and 75 R/min. The RBE of these X-rays were estimated to be 0.6 that of 200—400 kV X-rays.

According to Arnold, the paraventricular and supraoptic nuclei were "rather responsive" to the radiation. In 2 monkeys exposed to 3000 R and sacrificed 6 months later these two nuclei were almost selectively affected as far as the hypothalamus was concerned. In 1 monkey receiving 1500 R, "the selective effect . . . was observed to a lesser degree," and in 3 others, which received 5000—7000 R, the entire hypothalamus was damaged. A footnote in the article stated that comparable hypothalamic changes were noted in 5 other monkeys, but no details as to dosage, etc., were given. The incidence of selective involvement of the paraventricular and supraoptic nuclei in the 40 monkeys was not established.

In the Arnold-Bailey papers only the paraventricular nuclei were illustrated. As seen in these illustrations, about 50% of the nucleus on the two sides contained necrotic areas, which coalesced with one another. At the edge of lesions, severely damaged nerve cells were disappearing. It was stated that "all" the surviving nerve cells showed degenerative changes. Few if any reactive glia were found in the vicinity of affected areas. There was no mention of calcific material in the lesions or elsewhere. According to Arnold, "The mechanism for this somewhat selective effect of X-rays upon the paraventricular and supraoptic nuclei has not been determined. It would appear to be a degenerative effect resulting

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from X-irradiation." Arnold, Bailey and Harvey remarked that the hypothalamus "responds in a very unusual fashion in that the cells of the paraventricular and supraoptic nuclei are selectively affected . . ."

In a study of the brain in general in these animals it was found that at a dose of 3000 R the transirradiated cortex was damaged but not as severely as the paraventricular and supraoptic nuclei (Arnold, Bailey and Harvey). Most consistently damaged was the white matter of the cerebrum and brain stem. At both sites the white matter was speckled with discrete lesions. The major damage was described as in nerve fibers. Oligodendroglia showed nuclear pyknosis and cytoplasmic swelling soon after irradiation at 1500—3000 R (Arnold and Bailey), but no mention was made of the status of these cells with the advent of delayed radionecrosis. Astrogliosis occurred in the vicinity of damaged tissue in 6—8 months after irradiation at 3000 R, but was "rather moderate." This was taken to indicate "a definite impairment of the reactivity of the glial cells by radiation" (Arnold, Bailey, Harvey *et al.*). Another interpretation was that the "readily demonstrable radioselectivity for the white matter begins as a demyelinating process and proceeds, with time and increasing dose, to an actual necrosis of the myelin and axons . . ." (Arnold, Bailey, Harvey *et al.*). At 12 months postexposure (1500 to 3000 R), vessels in degenerated areas of white matter were found moderately thickened, while in the cortex they appeared unaltered. From this observation it was gathered that "the vascular changes and the obliteration of vascular channels were for the most part secondary to the death or degeneration of neural tissues, rather than a primary effect of radiation" (Arnold, Bailey and Laughlin). Further, it was stated that "the insignificant vascular changes cannot conceivably account for the damage to the neural elements" (Arnold, Bailey and Harvey).

The Arnold-Bailey reports seem the only ones available on delayed radionecrosis in the hypothalamus. The finding of hypothalamic damage in monkeys exposed to X-rays and γ-rays led us to take up the subject again. The report follows.

Material and Methods

Seven juvenile cynomolgus monkeys (*Macaca irus*), 4 females and 3 males, were used in this study. They were strapped in a lead-shielded chair allowing only the head to be exposed to the radiation source. The irradiation was accomplished in a single session, interrupted at the midpoint when the animals were rotated 180°. The radiation was directed to the sides of the head. However, the animals tended to look toward the source, and thus the frontal lobes were usually the most heavily exposed. All the animals received 2000 R at 50 R/min (air dose). Of the 7 animals, 4 were irradiated with a 250 kVp X-ray machine operating on 30 mA

with 0.5 mm Cu and 1 mm Al filtration. The half-value layer was 1.5 mm Cu. The radiation was given at 70 cm from the center of the animals' heads, at which distance the flux covered a 20×20 cm field. The heads of the other 3 animals were exposed to γ-rays from a teletherapy unit containing about 230 Curies of Co-60 at the time of irradiation. Under these conditions, 37 minutes were required to administer 2000 R. The midline X-ray dose was approximately $80\,\%$ of the air dose or of the proximal skin dose, or about 1775 R. In the case of the γ-radiation, it was given over the same time period but at a distance of 35 cm. The midline γ-dose was about 2015 R. Radiation and other data are given in the table. EEG and behavioral studies carried out in these animals are reported elsewhere (RIOPELLE *et al.* 1967). The animals either died or were sacrificed when moribund. Severe ulcerative and other lesions developed in the face in practically all the animals, and bronchopneumonia or pneumonitis in 3 (Cases 1, 3 and 4). Otherwise no significant visceral lesions were observed.

All the brains were fixed in $10\,\%$ formalin, embedded in celloidin, and serially sectioned at 30—40 μ. From each 30 sections, 3 succeeding sections were stained by cresyl echt violet, hematoxylin-van Gieson, and by the Woelke method for myelin, respectively. In selected sections, other staining or silver impregnation methods were used, as is brought out in the text.

Observations

Hypothalamus and Neighboring Structures

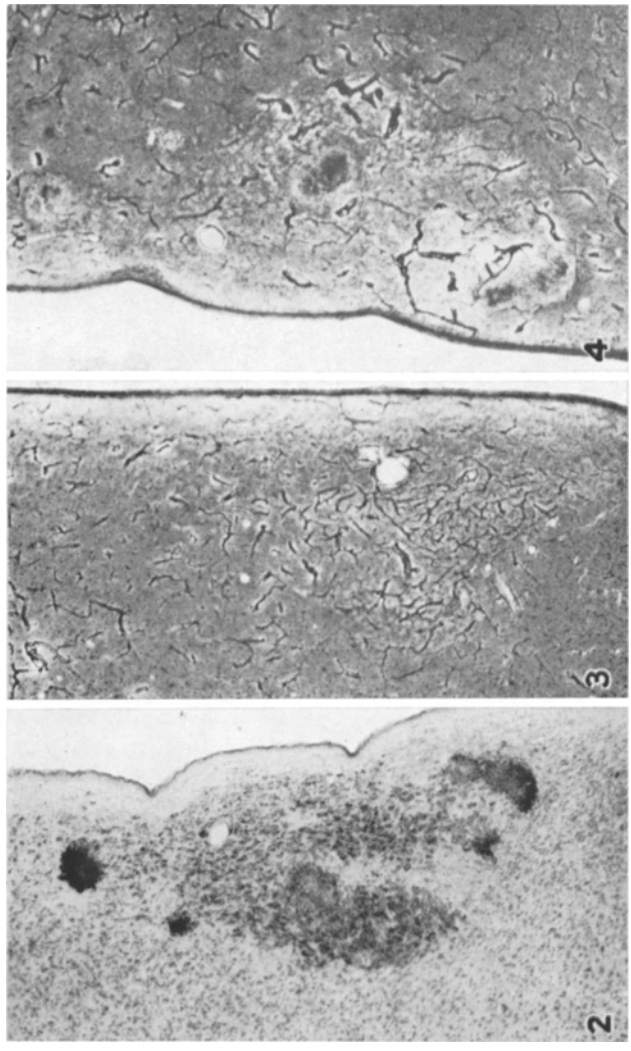
In the first 4 animals listed in the table, no changes were observed in the hypothalamus.

In *Case 5*, the supraoptic nucleus of one side was severely damaged (Fig. 1). It contained necrotic areas, between which were islands of degenerated supraoptic cells. The necrotic areas were coextensive upward into the lateral preoptic area of the hypothalamus, and above this lesion another focus of cellular necrosis was forming. Throughout these lesions were numerous reactive mesenchymal cells. Branches of vessels extending into the upper part of the more advanced lesion were distorted and apparently necrotic. In the subjacent optic tract, many mesenchymal cells were issuing from capillaries. The paraventricular nuclei were unaffected. Further, an area in the mamillothalamic tract of one side was severely damaged and was heavily infiltrated with activated mesenchymal cells. Vessels within and adjacent to the lesion were dilated. Isolated focal damage of white matter of this proportion was also noted elsewhere in basal structures, for example in fiber bundles in the amygdala.

In *Case 6*, lesions were encountered unilaterally at several sites, but not in the supraoptic nucleus. In the paraventricular nucleus, as seen in a

Fig. 1. Case 5. An area of cellular necrosis involves parts of the supraoptic nucleus (*lower two arrows*) and the adjoining part of the lateral preoptic nucleus. Above it, in the lateral preoptic nucleus, is another area of cellular necrosis, in which the damage is less advanced (*arrows*). X 52. Cresyl echt violet

Nissl preparation, the lesions were multifocal and were located both within the nucleus and along its border (Fig. 2). Most of the lesions were heavily infiltrated with calcific material. Lesions of the same kind at other levels contained abundant calcium salts (von Kóssa method), and in occasional lesions, iron salts as well (Gomori method). The section shown in Fig. 2 was destained and impregnated with silver by a modified Hortega method. (The section was reversed when mounted, so what appears the right side is actually the left.) The preparation, shown in Fig. 4, reveals thickening and dilatation of many of the vessels in the paraventricular nucleus. Most of the capillaries had disappeared. The control (unaffected) paraventricular nucleus is shown in Fig. 3. Damage of the paraventricular nucleus was limited three-dimensionally, as examination of neighboring serial sections revealed no changes in this nucleus. The anterior hypothalamic nucleus (at the level of the paraventricular nucleus) and the medial preoptic nucleus (in an area just beneath the anterior commissure) were also damaged. Each contained a small focus of heavily calcified tissue. Dilatation of vessels around some of these foci was striking. In the septal nucleus and adjoining subcallosal gyrus, besides calcified foci, there were areas of cell fading in which slightly dilated vessels and activated microglia were found; situated in the midst of such areas



Figs. 2—4. Case 6. Fig. 2. Paraventricular nucleus, as stained by cresyl echt violet. Most of the foci of necrosis contain calcific material. A vessel in the nucleus is dilated. X 28.5. The section was destained and impregnated by a modified Hortega method, and in mounting the section the sides were reversed. Fig. 3 shows the unaffected paraventricular nucleus, and Fig. 4 the damaged nucleus. X 40

were calcified vessels. Within or near most of the lesions were thickened vessels, and occasionally, telangiectasias as well.

In *Case 7*, the paraventricular nucleus was the only hypothalamic structure affected. This nucleus was damaged bilaterally. In a myelin preparation a number of pale areas were visible. In the companion Nissl preparation, nerve cells had disappeared from these pale areas. In the center of some of the areas thus affected a somewhat distended and tortuous vessels was found (Fig. 5). Reactive cells in such areas were very few.

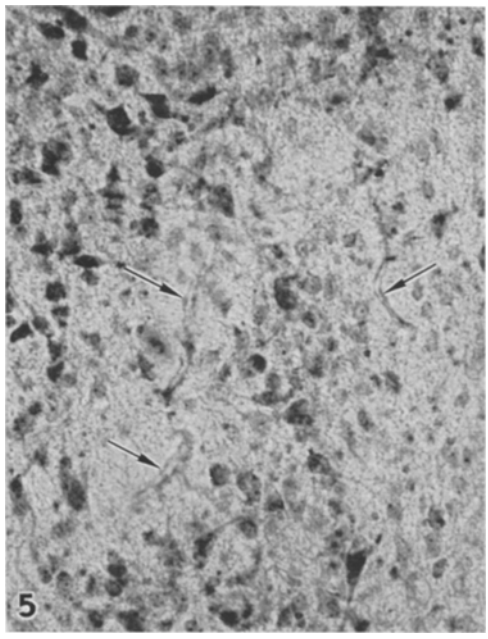


Fig. 5. Case 7. Paraventricular nucleus. The arrows point to somewhat dilated and tortuous vessels, around which nerve cells have disappeared. X 230. Cresyl echt violet

Brain in General

The animal dying in the shortest period of time (13 weeks) had purulent meningitis. No brain changes attributable to the irradiation were found.

From 17 weeks onward, pathological changes were consistently observed. In the X-irradiated animals the lesions were limited to the cerebrum, with the white matter of the frontal lobes (which, as mentioned previously, received the largest dosage) the most damaged, while in the γ-irradiated animals the white matter of the brain stem was also damaged, and in one of the animals, the cerebellar white matter as well (Table). Examination of sections with the unaided eye revealed, at the 17-week stage, very small lesions in the frontal white matter. Most of them were clearly oriented to the plane of vessels. At 18 weeks very small lesions were also seen, but most of the lesions had grown larger and were clearcut, and some had coalesced (Fig. 6). With the passage of time, the lesions continued to be multifocal and sharply circumscribed. However, in the frontal lobes they tended to be obscured by a pathological process characterized by demyelination. Further, at some levels of the frontal lobe in cases of longer duration, the white matter was devastated by advancing

Table. *Survival period and data on pathological changes in the brain. 0 signifies no pathological change; ±, very minor change*

Monkey No. Riop. No. AFIP Acc.	Type of Radiation	Survival Period (weeks)	Lesions in White Matter of			Lesions in		Aneurysms	Calcified Lesions
			Cerebrum	Brain Stem	Cerebellum	Cerebral Cortex	Hypothalamus		
1 126 989995	γ-rays	13	0	0	0	0	0	0	0
2 116 988872	X-rays	17	2+	±	0	±	0	0	1+
3 100 989992	γ-rays	18	2+	2+	0	0	0	2+	3+
4 104 989993	X-rays	20	2+	±	0	+	0	1+	1+
5 112 988871	γ-rays	20	3+	2+	3+	+	+	4+	3+
6 124 988873	X-rays	33	4+	0	0	+	+	1+	4+
7 118 989994	X-rays	35	4+	0	0	+	+	2+	3+

tissue necrosis. Under these conditions areas of the adjoining cerebral cortex were also heavily damaged. Cortical lesions independent of white-matter damage were also seen. Aneurysms (Table) and telangiectasias could usually be found, but were most frequent in the frontal lobes; in the γ-irradiated animals they were also seen elsewhere, often in little altered tissue. Finally, in most of the cases brain atrophy was evident. In such brains, vessels in many locations were dilated (Fig. 6).

As viewed microscopically, a wide spectrum of pathological change was encountered. Only certain lesions that have pertinence to the subject of this paper—i.e., the hypothalamic aspect of the problem—will be dealt with.

In the white matter, vessels were commonly found affected in the virtual absence of pathological change in the neighboring tissue. Thus, small assemblages of activated mesenchymal cells could be found lined

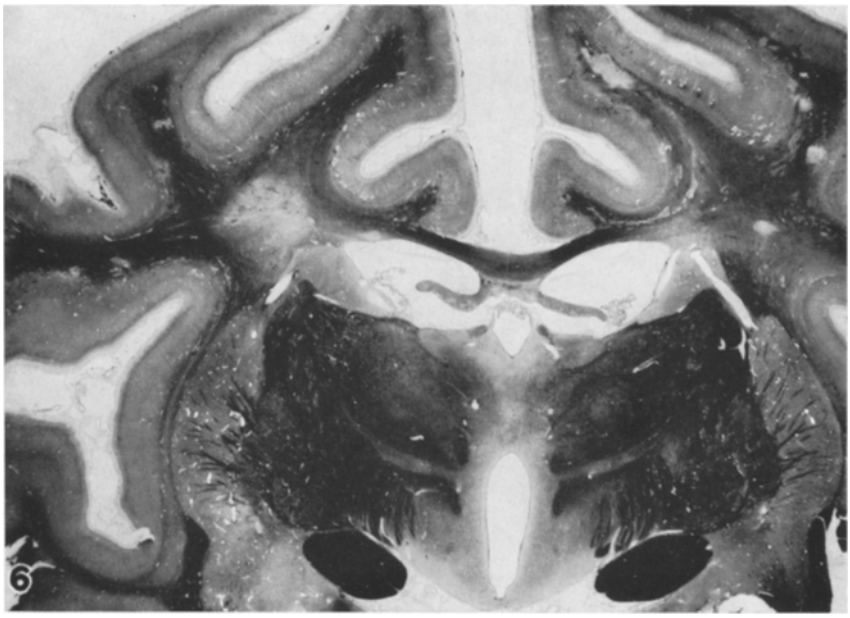
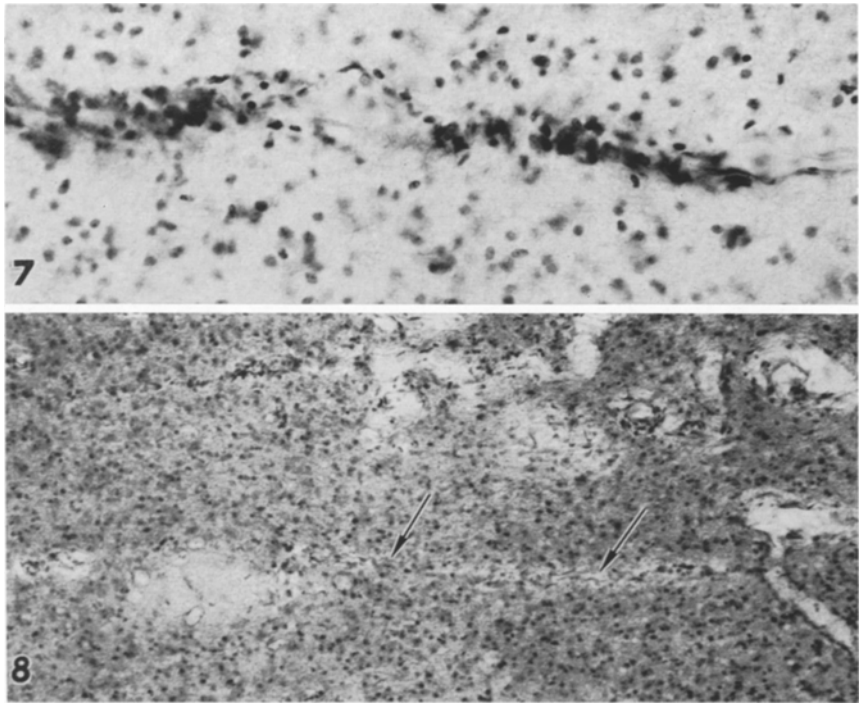


Fig. 6. Case 6. Frontal section showing lesions mainly in white matter. Some of the lesions are oriented in the same plane as stem vessels. Considerable brain atrophy has occurred. X 3.8. Woelke myelin method

up along capillaries. Or myriad mesenchymal cells emanated from vessels of capillary proportion, as in the optic tract in Case 5 (Fig. 1). Cells of some medium-sized vessels were hypertrophic and bizarre in appearance (Fig. 7). Frequently, the lumen of vessels was greatly widened (Fig. 8). In some areas the vessels were grossly thickened and distorted (as illustrated for the paraventricular nucleus in Fig. 4). Moreover, vessels exhibiting little change in caliber nonetheless showed cellular abnormalities. The presence of aneurysms and telangiectasias has already been mentioned. Also fairly frequent were calcified vessels, with an abundance of mineral-laden material in the adjoining, heavily damaged tissue.

The predominant lesion in the white matter included what may most appropriately be called "coagulative necrosis." Such lesions were commonly found perivascularly. This is illustrated in Fig. 9. Here, either myelin pallor or tissue destruction is to be seen around practically every vessel. The larger lesions shown in this photograph are presumed to have developed in the same way; it is suggested that in enlarging, the lesions escaped vascular bounds. Development of a small focus of coagulative necrosis in association with dilated vessels is shown in Fig. 8.



Figs. 7 and 8. Cerebral white matter. Fig. 7. The vessel is dilated, and bizarre cells are present along its course. X 300. Fig. 8. Vessels are enormously dilated. A small lesion is developing in relation to them. To the left is a coagulative lesion in the midst of which are dilated vessels. Spatially related to this lesion and apparently coursing from the dilated vessel is a small, abnormal vessel (*arrows*) which is apparently a branch of the dilated vessel. X 130. Cresyl echt violet

Another kind of lesion commonly observed in the white matter consisted in spongiform tissue necrosis. Lesions of this kind were sharply circumscribed. They were not seen perivascularly, but, instead, occupied capillary beds. This kind of lesion was not found in the hypothalamus or in the cerebral cortex.

Oligodendroglia were commonly involved in early stages of lesion development in all the cases. However, little needs to be said about the changes as they are described elsewhere (HAYMAKER *et al.*, 1967). Suffice it to say that glycogen appeared in these cells in earlier stages of their demise, and that breakdown of the oligodendroglia-myelin unit, which was vascular-dependent, appeared to be the basis of the development of some of the coagulative lesions.

In the cerebral cortex, the predominant lesion was of the coagulative type. Such lesions were multifocal, in different stages of evolution, and

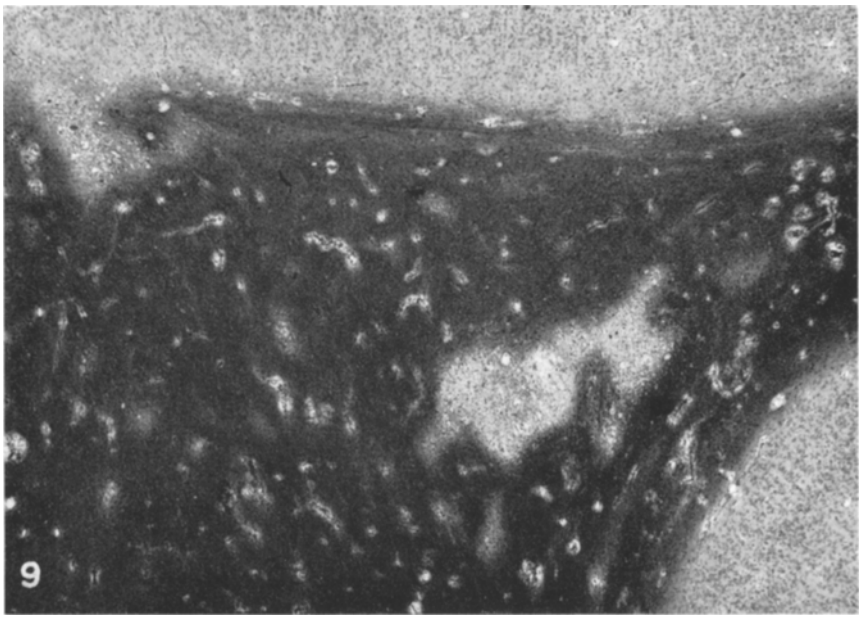
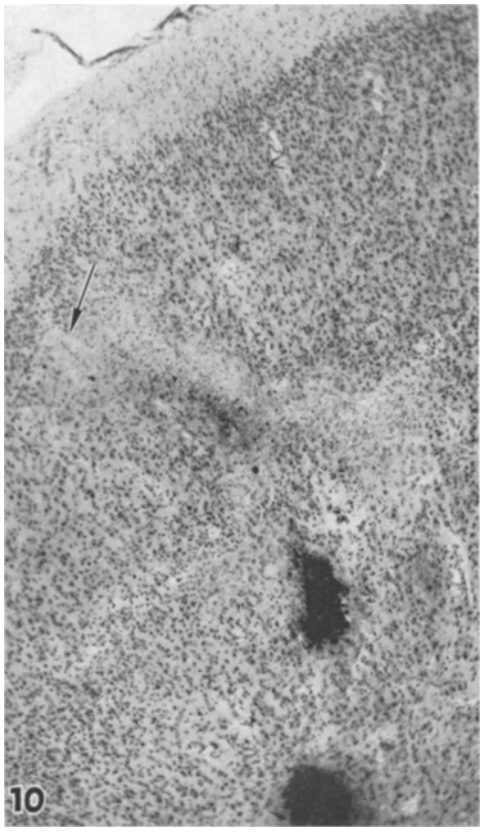


Fig. 9. Case 5. Frontal lobe. Areas of tissue pallor surround many of the vessels. Around some vessels the parenchyma has been damaged. Larger areas of necrosis are also present. One of the lesions is continuous into the cortex. X 40. Woelke myelin method

usually of sinuous pattern. Smaller coagulative lesions could be found centered on vessels; deposits of calcareous material in damaged tissue were also frequent (Fig. 10). Occasionally the tissue surrounding penetrating cortical vessels was found damaged throughout three or four laminae. Vertical streaks of coagulative necrosis were occasionally seen in the cortex in areas in which vessels in the overlying meninges were dilated and had sclerotic walls. In silver-impregnated material, larger vessels were found much thickened, such that they were tortuous and, in places, buckled. A further observation was that plasmatic material was issuing from vessels of fairly normal appearance and overrunning and destroying cortical tissue (Fig. 11). This was, however, infrequent.

Discussion

Lesions appearing in the hypothalamus were no different from those occurring in the cerebral cortex, and they were no different from those developing in the white matter, except that the lesions here were of a more diverse character than in the other two sites. This is to be expected from the greater tendency of white matter to develop lesions.



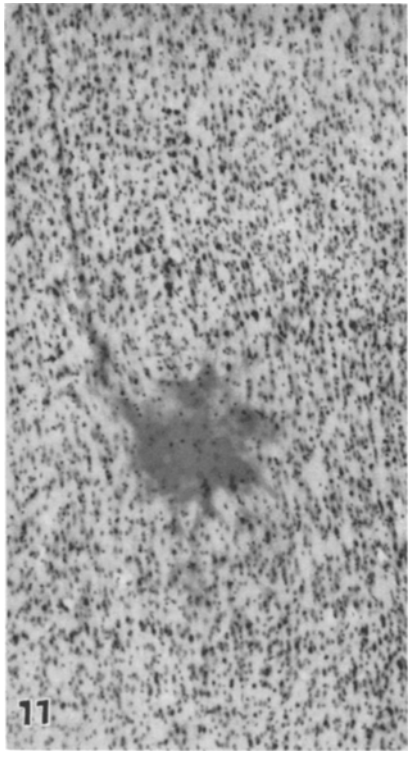


Fig. 10. Case 7. Frontal cortex. Multifocal cellular necrosis of sinuous pattern. Smaller areas of necrosis surround vessels (*arrow*). Some foci contain calcareous material. X 70. AFIP Neg. 62-922.
Fig. 11. Case 4. Plasmatic material has escaped from the vessel and destroyed some of the tissue. X 100. Cresyl echt violet

One of the most impressive pathological changes in this series was the dilatation of vessels. The dilatation was noted not only in the hypothalamus, white matter and cerebral cortex, but also in the meningeal vessels. It was not easy to determine the basis of this dilatation. Direct radiation injury to vessels could be postulated as its basis—in some instances at least—but there were no criteria secure enough to allow any particular change to be singled out as radiation-induced, except for aneurysmal formation. The dilatation could have been secondary to the cerebral atrophy that was evident in most of the cases, or the dilatation could have been the result of back pressure resulting from obstruction, of whatever cause, in the capillary-venous system. Regardless of how the dilatation developed, the associated stasis, we believe, was pathogenic.

Severe vascular permeability disturbance, whatever the basis, could account for lesions such as illustrated in Fig. 9.

Another manifestation of altered vascular permeability was the outpouring of mineral-laden fluid into the tissue. This was a common disturbance. At some levels of the frontal lobe in Case 7, calcific deposits dotted the white matter and also some areas of the cortex, in the virtual absence of other changes.

Moreover, there were vessels of relatively normal appearance which were functionally defective. This is illustrated in Fig. 11. Pertinent in this connection was an observation by Scholz, Ducho and Breit (1959) and Scholz, Schlote and Hirschberger (1962), in a study of the delayed radiation reaction in the spinal cord of rabbits, in which areas of the white matter were necrotic. Although the grey matter in the cord was little altered, and although the vessels were practically of normal appearance, trypan blue given intravitally permeated practically all the grey. Thus, there may be functional disturbances in vessels of the irradiated CNS without demonstrable morphological manifestations thereof.

Before turning to the hypothalamus a word needs to be said about the knotty problem of the influence of direct radiation injury of the parenchyma on delayed lesion development. It has been shown and confirmed that radiation in the dose range used in the present study can directly injure the CNS. But there is no clear evidence that long-incurred brain damage is in itself the basis of delayed radionecrosis. This is a view supported by the experimental observations of Zeman, Carsten and Biondo (1964). However, it appears that brain damage can give rise to delayed radionecrosis secondarily through the stasis and associated hemodynamic disturbances that develop as a consequence of brain atrophy. Occurrence of hemodynamic disturbances as a major factor in causing delayed radiation necrosis is in accord with the view of Scholz and his colleagues (Lyman, Kupalov and Scholz, 1933; Scholz, 1934, 1949, 1957; Scholz, Ducho and Breit, 1959; Scholz, Hager *et al.*, 1961; Scholz, Schlote and Hirschberger, 1962), although their view was not formulated entirely in the same way as ours. Zeman *et al.* (Zeman 1963, 1964, 1966a—c; Zeman, Carsten and Biondo, 1964), on the basis of tritiated thymidine and tritiated cytidine studies, have proposed an alternative hypothesis to explain the development of delayed radionecrosis. Comment is, however, not necessary here, as the hypothesis is discussed elsewhere (Haymaker *et al.* 1967).

Coming now to a consideration of the hypothalamic lesions, Arnold, Bailey and Harvey (1954), in their statement dealing with the genesis of lesions in the paraventricular and supraoptic nuclei (cited in the foregoing), apparently concluded that necrosis of cells of these nuclei was due directly to the radiation. No working hypothesis was provided as to how

radiation injury of the nerve cell could become manifest after a latency of some months. ZEMAN (1966a and b), admittedly on the basis of conjecture, suggested that damage of cells in these nuclei could be tied up with their close proximity to capillaries. This was in the sense that oxygen tension in these cells should be relatively high, a factor which, according to him, should predispose them to radiation injury. Our Fig. 5, showing that nerve cells next to vessels were disappearing, could be cited in support of this view, as could all the paravascular lesions observed, including those in the white matter. That an oxygen effect can be obtained in the CNS under normal atmospheric conditions still needs, however, to be demonstrated.

ZEMAN singled out denseness of the capillary bed as the basis of the selective involvement of the paraventricular and supraoptic nuclei observed by ARNOLD, BAILEY *et al.* However, in our series the factor of capillary density could not have been of much over-all importance, as lesions involved hypothalamic nuclei indiscriminately. If capillary density were a determining factor in lesion development, then the supraoptic nucleus should carry the highest incidence of damage, as it has an even richer capillary bed than that possessed by the paraventricular. ARNOLD, BAILEY *et al.* did not illustrate the supraoptic nucleus, and thus we have no basis for comparing their observations with ours. The supraoptic nucleus was damaged in only one of our cases, and then only focally. The paraventricular nucleus was selectively injured bilaterally in one of the cases (Case 7), also focally, without any change occurring in the supraoptic nucleus. An explanation of the differing vulnerability may be sought in the blood supply of these two nuclei. In the monkey, FINLEY (1940) observed that a branch originating from the anterior cerebral artery passes medial to the optic tract, gives off branches to the supraoptic nucleus, then proceeds upward to supply the paraventricular nucleus. The supraoptic nucleus is drained by the basal venous system, and the paraventricular nucleus by the internal cerebral venous system. The vascular setup is thus such that alteration in blood vessels in different parts of the system could lead to differing effects upon these two nuclei. That random radiation-induced damage of vessels was the basis of the lesions in our series appears plausible. Focal distribution of the lesions supports this possibility.

From the foregoing it seems evident that the genesis of lesions in the hypothalamus is fundamentally no different than elsewhere in the CNS. The sites at which lesions develop in the CNS would seem to be determined by the regions of the vasculature in which hemodynamic crises occur. Lesion development must also be dependent in some degree on metabolic tissue requirements at the time the hemodynamic crises are occurring.

The hypothesis presented here could account for a number of variables associated with the development of delayed radiation necrosis, such as outcropping of lesions at different times in the same brain, enlargement of lesions once they had formed, and the wide range in the latency at which radionecrosis occurs.

Summary

This report deals with delayed pathological changes observed in the brains of monkeys receiving X- and γ-radiation to the head in a dose of 2000 R given at 50 R/min.

The pathological changes observed in the hypothalamus and the rest of the brain strongly suggested a "vascular factor" as of overriding pathogenic importance in lesion inception.

Zusammenfassung

Bei sieben jugendlichen Macacus-Affen wurden späte neuropathologische Veränderungen des Gehirns nach γ- und X-Bestrahlung des Kopfes beschrieben. Die Dosierung betrug 2000 R bei 50 R pro Minute.

Die Veränderungen im Hypothalamus wurden im einzelnen dargestellt. Starke Gefäßerweiterungen sprechen für einen vascularen Faktor der Strahlenschädigung.

The brain sections were obtained from the Armed Forces Institute of Pathology, Washington, D. C., where preliminary studies were carried out by Dr. P. Lampert and Dr. R. P. Davis. AFIP accession numbers are indicated in the table.

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