ies have been made in an attempt to discover a relation between pressor response and chemical structure, carried out on many isolated organ preparations and animals(3). However, no thorough reports contrasting the response of normotensive and hypertensive animals has appeared. Such a correlation would seem to be of value in a search for the possible site of metabolic dysfunction in hypertension. In the present investigation the effect of representative compounds has been utilized: isoamylamine—a branched chain aliphatic amine, phenethylamine—an aromatic amine, tyramine—a phenolic aromatic amine, arterenol—a catechol derivative with an aliphatic hydroxyl group. In the case of isoamylamine, normotensive rats gave the usual pressor response. However in hypertensive rats a notched curve was obtained—an initial increase, a temporary fall, and a secondary increase in blood pressure. This difference has also been noted in comparison of normotensive and hypertensive patients, the latter in some cases showing only a decrease in blood pressure when isoamylamine was injected intravenously. Due to inherent errors in the bioassay method and the progressive nature of hypertension fine differences in structure may not be appreciated but the more important ones can be detected by procedures such as those here reported.

Explanation of these results is difficult in the light of present knowledge. Increased sensitivity of hypertensive animals to pressor agents is explicable upon application of known laws relating peripheral resistance to arteriolar diameter; when arterioles are already constricted, further constriction by a drug causes much greater changes in resistance than when they are dilated. The results found with arterenol are therefore in agreement with this hypothesis. The paradoxical effect of isoamylamine is not. One possible explanation involves the substitution of a substance with slight pressor activity for one with marked activity. If renal hypertension in the rat is accompanied by circulating pressor substances of considerable vasoactivity, "flooding" the circulation with a competitive substance of less activity would give rise to a lessened response. Isoamylamine may act in this manner, although a cardiac effect may be important.

Summary. The pressor response of various amines in anesthetized normotensive and hypertensive rats have been studied. The two groups of animals responded differently to different amines. Whereas phenethylamine and tyramine elicited the same degree of elevation of blood pressure in normotensive and hypertensive rats, arterenol and epinephrine caused greater responses and isoamylamine effected much smaller responses in the hypertensive animals.

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The Use of Radon Seeds to Produce Deep Cerebral Lesions.* (17980)

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Experimental neurophysiology has long made use of the classical method of ablation of various nervous structures and observation of subsequent alteration in function to evaluate the physiological significance of these structures. No problems are encountered when the structures lie on the surface of the brain or spinal cord. When they are deep in the brain substance, however, difficulties are presented in localization and mode of destruction. Although several different technics are available for accomplishing these things in the depths without disturbing superficial structures beyond the small lesion necessary to introduce an instrument, they all have attendant features which are not entirely satisfactory. Among the technics used in the past are injection of chemical substances(1),

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destruction with a knife(2), removal by suction(3), thermocoagulation(4), freezing(5), and electrolytic destruction(6).

In recent years, the method most commonly used has been the electrolytic one, where a stigmatic electrode (anode) is placed deep in the brain and an electric current (DC) passed between it and a large remote electrode (cathode). This method has several disadvantages: *viz.*, there may be vascular spread from a large lesion made at one sitting; the shock of a quickly produced lesion may be fatal to the animal; the size of the lesion produced is difficult to control and because of the danger of vascular spread can never be large. Therefore, we have adapted a method which produces a lesion more gradually, that is with less shock, and which permits the production of a large lesion with a single puncture, obviating the necessity of inserting multiple electrodes into the brain. It is the method first used by Edwards and Bogg(7), who worked on dogs and made their lesions in the corpus striatum. It seemed worth while to us to modify the method and explore its suitability for producing stereotaxically controlled lesions.

Our experiments were done on monkeys (*Macaca mulatta*) under nembutal anesthesia. The animal's head was fixed in a stereotaxic instrument† and draped for aseptic surgery. The needle-holder of the instrument, set to hit the desired structure, introduced a hollow needle into the brain. A gold radon seed was carried just inside the tip of the needle and a stylet was used to deliver the seed into the brain. The surgical procedure consisted of incising the skin, trephining a hole in the skull approximately 6 mm in diameter, and cutting a piece of the dura no more than 1.5 x 1.5 mm. Following the operation, the monkeys were observed for changes in neurological status. All the animals in this study had needles directed into the midbrain 30 degrees anterior to the traditional Horsley-Clarke plane, which placed the needles roughly in the long axis of the brain stem. We will cite the protocol of one of our monkeys to illustrate the findings in our series: A female weighing 2.9 kg was observed following the placement of seed 2 mm in length containing 2.82 mc of radon.

On the day following operation, her left pupil was found to be fully dilated and her head tilted so that it rested on her right shoulder. A postural tremor was observed at the elbow and shoulder of the right upper extremity. This tremor was not continuous but occurred in bouts. On the second post-operative day, both pupils were dilated and both upper lids were ptosed. Her head remained tilted and there was deviation of the upper spine to the right. She moved with a squatting posture and kept circling to the right. Pain sensation was absent in the right leg and diminished in the right arm. An occasional bout of postural tremor was observed in the left hip and knee. There was weakness in the right arm and right leg. On the third post-operative day all tremor disappeared. On the fourth post-operative day she was observed to sit with her head hanging. The weakness of the right arm and leg had progressed, but motor function in the left extremities remained good. Both knee jerks were a little brisk, but there was no clearly defined spasticity. The left extremities, which she used to defend herself, did not appear to have any dyssynergia. No pain sensation was appreciated in the right arm and leg. Because of these definite neurological changes,

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† Lab-Tronics, Inc., Model No. G-101.

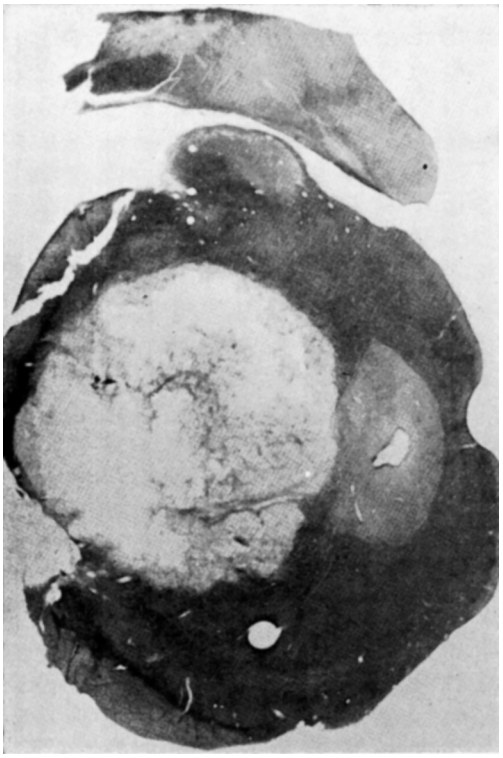

FIG. 1.

the monkey was sacrificed on the fourth postoperative day, and the brain perfused with saline followed by 10% formalin. X-ray pictures were made of the skull to show the position of the radon seed, and then the brain was removed for study.

Histological examination of this brain showed a spherical lesion (Fig. 1) which measured 1 cm in diameter, having its center in the midbrain at the level of emergence of the third nerves. The lesion destroyed all of the left and most of the right oculomotor nerve, all of the red nucleus and decussation of the superior brachium and the medial half of the left substantia nigra. The medial tegmentum adjacent to the substantia nigra and a large part of the lateral mesencephalic tegmentum on the left side, and the ventral portion of the central grey were also destroyed. The lesion extended cephalad on the left, destroying structures lying dorsal to the mammillary bodies and medial to the subthalamic nucleus, including the fasciculus thalamicus and median center. Caudally, destruction extended into the tegmentum of the pons at the level of the inferior colliculi. The lesion appeared to be an acute necrosis without vascular spread, and the neurones which surrounded the lesion appeared normal. The zone of cellular reaction in the surrounding brain was very small. The destroyed area thus had a "punched-out" appearance because the necrosis within the lesion was so complete. Except for the persistence of short stubby remnants of some of the larger blood vessels, no structure within the lesions could be identified.

Thus the following features are salient in this method of making a lesion. First, a large lesion can be produced with a single small wound of entry. Second, the lesion is produced so slowly that nervous tissue is not subjected to abrupt change, with resultant "shock." Hence, a larger lesion is possible than can be produced in one sitting by electrolytic means. Third, the lesion can be located easily during life by X-ray (the radon seed is radio-opaque). And fourth, the size of the lesion produced can easily be controlled by choosing the dose of radon.

For these reasons, the method outlined above seems to offer definite usefulness in the production of animals with deep chronic lesions. We would also like to suggest this method to the neurosurgeon, especially since there has recently appeared on the market an adequately designed stereotaxic instrument for man.‡ We see no reason why the stereotaxic technic cannot be used in the attack on human cerebral dysfunction where destruction of certain tracts or nuclear structures deep in the brain are considered to be of value. In fact, stereotaxically placed radon seeds might offer an approach to the treatment of deep neoplasms of the thalamus or basal ganglia.

Summary and conclusions. 1. Stereotaxically placed radon seeds in the brains of monkeys produced well controlled lesions suitable for studying certain aspects of cerebral physiology. 2. The technic described, which requires only a minor surgical procedure, should be considered for producing deep lesions and for attacking deep tumors in the human brain.

‡ Lab-Tronics, Inc., Model No. G-111.

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