Stimulation of Limbic System of Brain in Waking Animals

Phylogenetic and cytoarchitectural studies, together with recent physiological investigations, suggest that the limbic system represents an early neural development involved in the higher control of the autonomic nervous system and in affectively determined behavior (*1*, *2*). The limbic system has a marked influence over the viscera controlled by the autonomic system; hence the designation "visceral brain" is applied to it (*1*).

This paper (*3*) summarizes our studies on 29 cats and 13 monkeys (*Macacus*), in which multilead electrodes were implanted in both cerebral hemispheres in different parts of the limbic system (amygdala both anteromedial and basolateral nuclei, pyriform cortex, hippocampus, temporal tip, posterior orbital gyrus, and anterior cingulate gyrus). After recovery, these areas were stimulated electrically in unanesthetized waking animals. The parameters of stimulation used were 30-cycle-per-second square waves pulses of 0.2- to 1-millisecond duration and 3- to 8-volt intensity.

Affective behavior of the animals showed marked and varied changes on stimulation of different regions. Stimulation of temporal lobe structures, excluding the tip, made the majority of the animals agitated and fearful, but quieted some of them. Temporal tip stimulation of cats made them very irritable. Stimulation of temporal tip in monkeys and stimulation of posterior orbital cortex just rostral to temporal tip in cats made them very vicious and violent. On the other hand, cats with electrode locations further removed from the temporal tip, as well as monkeys, became very quiet during posterior orbital stimulation. Stimulation of the anterior cingulate caused convulsions followed by a typical rage reaction.

Certain somatic movements involving the ipsilateral facial, eyelid, orbital, and oral muscles, and rarely the limb muscles, and also dorsal retraction of the head were obtained by stimulation of all these regions. Contraversive turning of the head (*4*) was obtained only in 6 cats by stimulation of the amygdala, orbital cortex, and cingulate gyrus. Organized movements of "eating" automatisms (*5*) (sniffing, licking, chewing, biting, and chop-licking) were also obtained by stimulation of all the regions. The food intake was not increased by stimulation.

Stimulation of widespread points in all these structures produced signs of autonomic activity that included lachrymation, salivation, pupillary changes, movements of nictitating membrane, and more rarely urination and defecation. The volume of gastric secretion, as well as its HCl (free and total) and pepsin contents, was both increased and decreased by such stimulation; gastric motility was inhibited by stimulation of the temporal lobe structures, and both increased and inhibited by stimulation of the posterior orbital and anterior cingulate gyri. There was usually a rise in blood sugar level resulting from stimulation of all the limbic structures in the monkey; in the cat, there was a rise resulting from stimulation of all these structures except the anterior cingulate. Fall in blood sugar resulted only from stimulation of anterior cingulate gyrus in the cat. Changes in blood pressure were elicited on stimulation of all the different regions. In the majority of cases, stimulation of temporal lobe structures produced a fall, while stimulation of the temporal tip and posterior orbital and anterior cingulate gyri produced a rise. Changes in the respiration, on the other hand, could only be elicited from few points stimulated, and there was no relationship between these and the blood pressure changes. There was usually an inhibition of respiration (even apnoea in some) from stimulation of the anteromedial amygdala, while stimulation of different points in the orbital cortex, anterior cingulate, and temporal polar regions produced both inhibition as well as acceleration (*6*).

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References and Notes

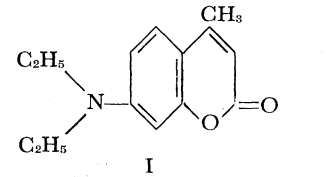
1. P. D. MacLean, *Psychosom. Med.* 11, 338 (1949).
2. J. F. Fulton, *Frontal Lobotomy and Affective Behavior* (Norton, New York, 1951).
3. This investigation was supported by a grant from the Indian Council of Medical Research. The equipment was supplied by the Rockefeller Foundation of New York.
4. B. R. Kaada, *Electroencephalog. and Clin. Neurophysiol.* Suppl. 4, 235 (1953).
5. P. D. MacLean and J. M. R. Delgado, *ibid.* 5, 91 (1953).
6. Detailed results of these investigations will be published in *Indian J. Med. Research.*

7 July 1955

New Liquid Scintillation Phosphors

A number of "whiteners" used in laundry detergents and some other related compounds have been examined for liquid scintillation activity (*1*). Although none of the compounds reported here show properties superior to the best phosphors now available, they represent entirely new classes of compounds in this field and may, therefore, be of interest as a starting point for better compounds and in the study of the liquid scintillation process itself.

About 40 compounds were obtained from five companies: E. I du Pont de Nemours and Company; Ciba Company, Inc.; General Aniline and Film Corporation; American Cyanamid Company (Calco); and the Hilton-Davis Chemical Company. Two of these compounds showed special promise. These were 7-diethylamino-4-methylcoumarin (I) and 2(*p*-dimethylaminophenyl)benzthiazole (II). Compound I was submitted by several companies and can be obtained commercially from a number of sources. Compound II was submitted by the Jackson Laboratory, Organic Chemicals Department, E. I. du Pont de Nemours and Company.



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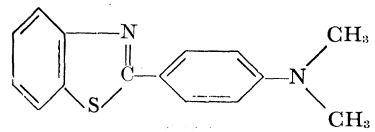

II

At the time these measurements were made, the liquid scintillator that gave best results in our laboratory consisted of 0.4-percent 2,5-diphenyloxazole (PPO) and 0.002-percent 1,6-diphenylhexatriene (PPHT) in toluene. The mean pulse height obtained using a cobalt-60 source with this phosphor, flushed with nitrogen, will be referred to as 100 percent. Since these measurements were made, a solution of 0.4-percent PPO and 0.01-percent 1,4-di(5-phenyl-2-oxazolyl)benzene (POPOP) has been used, which gives on this scale a pulse height of 121 percent.

Various preparations of compound I, tested as 0.4-percent solutions in toluene, gave pulse heights from 86 to 100 percent. Compound II gave pulse heights of 90 percent. These compounds were used as received without special effort at further purification. The addition of a secondary solute such as PPHT or POPOP had little or no effect on the scintillation properties of these solutions. In all cases, flushing with nitrogen to remove air increased the pulse height approximately 30 percent.

A number of other compounds showed less promise, but they still showed measurable scintillation activity. These included other amino coumarin derivatives, an amino derivative of benzoxazole, and a derivative of imidazolone.

A considerable number of compounds that were measurably soluble in water were screened for scintillation activity in water. Except for Cerenkov pulses, no activity was observed in any case, al-

though several compounds showed brilliant blue-violet fluorescence under ultraviolet excitation. To my knowledge, all toluene-soluble substances that exhibit fluorescence in the neighborhood of 4000 A and are not colored in this region are more or less good scintillators. Thus, we must conclude that one or more steps of the chain involved in the scintillation process cannot occur in ordinary aqueous solution. Some "shot" experiments have been made with aqueous solutions of these compounds to which additives such as inorganic ions and simple organic substances have been added. None of these gave positive results.

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References and Notes

1. I wish to thank John Marshall of the Institute for Nuclear Studies for suggesting the examination of these compounds. And I also thank the companies that so generously furnished samples for their cooperation in making these measurements possible. This research was supported under a contract with the Office of Ordnance Research.
2. F. N. Hayes and R. G. Gould, *Science* 117, 480 (1953). I am indebted to Hayes for a private communication on POPOP.

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Radiosensitivity of Anoxic Skin in Relation to Temperature

Reduced temperature in mammalian skin during exposure to ionizing radiations is accompanied by reduced radiosensitivity. This is interpreted in terms of an accompanying reduction in vascular supply. The radiosensitivity-modifying effect of alterations in vascular supply is ascribed to accompanying changes in oxygen tension; in effect, the protective influence of reduced temperature is attributed to the anoxic condition that it promotes. This view is supported by the radioresistance-enhancing effect of anaerobiosis in other protoplasmic systems (*1, 2*). However, there appear to have been no studies of the effect of temperature, during irradiation, on the radiosensitivity of skin when variations in oxygen tension are simultaneously precluded. This report is concerned with this question (*3*).

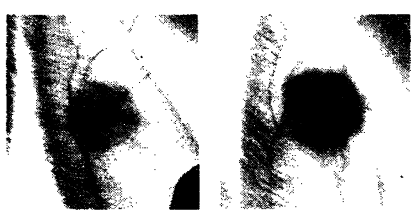

Fig. 1. Typical erythematous reaction 1 week following exposure to 28,800 r in a cooled tissue area (left) and in a warmed tissue area (right).

Homologous areas of the ears of female albino rabbits were simultaneously dehematized and conditioned to different temperatures shortly prior to and during exposure to heavy doses (up to 28,800 r) of soft x-rays (50 kv; 5 ma; 3600 r/min; beryllium window). Intensity of the erythema at 24 hours, 1 week (Fig. 1), and 2 weeks subsequent to exposure and the severity of later lesions, up to 8 weeks subsequent to exposure, were used as criteria of radiation damage. Each area was dehematized for 3 minutes prior to temperature regulation; then followed 10 minutes of combined dehematization and temperature regulation; this, in turn, was followed by 8 minutes of irradiation; the area was then released. Only a single area on any one ear was employed.

The technique is diagramed in Fig. 2. Tissue temperature was regulated by the temperature of the water flowing through the copper chamber. Dehematization was induced by compression; we employed a weight of 1140 g. Tissue temperatures were measured with a thermocouple. The beryllium compression surface insured maximum transmission of x-rays to the tissue. The dehematized area measured 218 mm^2; the irradiated area, in the center of the former, measured 95 mm^2. The fact that circulation was eliminated was demonstrated by injecting Evans blue in the artery of controls; no coloration appeared in the compressed area after this injection. Controls were effected on the opposite ear of one and the same experimental animal; in these, no untoward responses occurred.

This report is based on observations on about 30 warmed and 30 cooled tissue sites. In several instances, the radiation dose and the period of induced ischemia and temperature regulation were less than indicated; these experimental variations did not, however, essentially affect the over-all pattern of response. In general, the radiosensitivity of the anoxic tissue was found to be definitely reduced following irradiation at the lower temperature. The postirradiation responses, at various times after irradiation, of cooled (about 10°C) and warmed (about 39°C) tissue areas that were exposed to 28,800 r follow.

1) At 24 hours after irradiation: in 82 percent of the areas the intensity of the erythema was distinctly less in the cooled areas than it was in the warmed areas.

2) At 1 week after irradiation: in 88 percent of the areas the differential in erythematous response was the same as that described for 24 hours, but the contrast was decidedly greater (Fig. 1).

3) At 2 to 3 weeks after irradiation: with progressing complexity of the lesions, warmed areas continued to exhibit the more severe reaction; this was especially reflected in a corona of inflammation

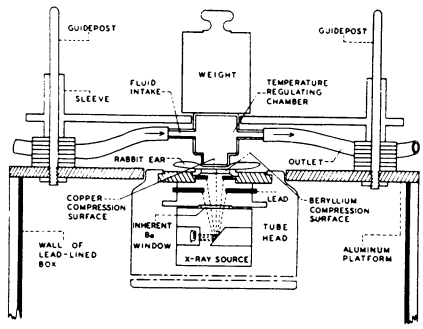

Fig. 2. Device by means of which anoxia, temperature-regulation and irradiation are simultaneously effected in localized areas of the rabbit ear.

peripheral to the irradiated area; this pattern prevailed in 90 percent of the areas.

4) At 4 to 7 weeks after irradiation: the same pattern of response continued and was evident in 96 percent of the areas. At 4 weeks, 40 percent of the warmed areas exhibited sequestration of the irradiated area (perforation); there was no sequestration in cooled areas. At 5 weeks, 83 percent of the warmed areas and 54 percent of the cooled areas exhibited sequestration. After sequestration, the corona of inflammation persisted for a considerable time in warmed areas but disappeared rapidly in cooled areas.

5) At 8 weeks after irradiation: there was total sequestration of the irradiated area in all warmed areas, and the perforation was always significantly larger than that occurring in cooled areas; 60 percent of the cooled areas exhibited perforation significantly smaller than the irradiated area; the remainder exhibited extremely small perforation or none at all.

These observations are offered as evidence, possibly the first of its kind, that the temperature prevailing in anoxic mammalian tissue at the time of irradiation is a significant dose-effect modifying factor.

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References and Notes

1. H. M. Patt, *Physiol. Revs.* 33, 35 (1953).
2. We demonstrated earlier, specifically for the rabbit ear, the respectively protective and compromising effect of cooling and warming during irradiation; we also demonstrated the protective effect of ischemia. J. P. O'Brien *et al., Anat. Record* 117, 530 (1953).

3. Work performed under U.S. Atomic Energy Commission contract No. AT(11-1)324 with Marquette University. We were aided (preliminarily) by the Milwaukee Division of the American Cancer Society. The x-ray equipment was provided by the X-Ray Department, General Electric Co. The assistance of Barbara Herbes and Phyllis Galasinski is gratefully acknowledged.

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