tion were randomly intermixed within the same block.

Each trial began with a warning tone, which was followed half a second later by the presentation of a stimulus pair and the simultaneous onset of a timer. The lever-pulling response stopped the timer, recorded the subject's reaction time and terminated the visual display. The line drawings, which averaged between 4 and 5 cm in maximum linear extent, appeared at a viewing distance of about 60 cm. They were positioned, with a center-to-center spacing that subtended a visual angle of 9°, in two circular apertures in a vertical black surface (see Fig. 1, A to C).

The subjects were instructed to respond as quickly as possible while keeping errors to a minimum. On the average only 3.2 percent of the responses were incorrect (ranging from 0.6 to 5.7 percent for individual subjects). The reaction-time data presented below include only the 96.8 percent correct responses. However, the data for the incorrect responses exhibit a similar pattern.

In Fig. 2, the overall means of the reaction times as a function of angular difference in orientation for all correct (right-hand) responses to "same" pairs are plotted separately for the pairs differing by a rotation in the picture plane (Fig. 2A) and for the pairs differing by a rotation in depth (Fig. 2B). In both cases, reaction time is a strikingly linear function of the angular difference between the two three-dimensional objects portrayed. The mean reaction times for individual subjects increased from a value of about 1 second at 0° of rotation for all subjects to values ranging from 4 to 6 seconds at 180° of rotation, depending upon the particular individual. Moreover, despite such variations in slope, the *linearity* of the function is clearly evident when the data are plotted separately for individual three-dimensional objects or for individual subjects. Polynomial regression lines were computed separately for each subject under each type of rotation. In all 16 cases the functions were found to have a highly significant linear component ($P < .001$) when tested against deviations from linearity. No significant quadratic or higher-order effects were found ($P > .05$, in all cases).

The angle through which different three-dimensional shapes must be rotated to achieve congruence is not, of course, defined. Therefore, a function like those plotted in Fig. 2 cannot be constructed in any straightforward manner for the "different" pairs. The *overall* mean reaction time for these pairs was found, however, to be 3.8 seconds—nearly a second longer than the corresponding overall means for the "same" pairs. (In the postexperimental interview, the subjects typically reported that they attempted to rotate one end of one object into congruence with the corresponding end of the other object; they discovered that the two objects were *different* when, after this "rotation," the two free ends still remained noncongruent.)

Not only are the two functions shown in Fig. 2 both linear but they are very similar to each other with respect to intercept and slope. Indeed, for the larger angular differences the reaction times were, if anything, somewhat shorter for rotation in depth than for rotation in the picture plane. However, since this small difference is either absent or reversed in four of the eight subjects, it is of doubtful significance. The determination of identity of shape may therefore be based, in both cases, upon a process of the same general kind. If we can describe this process as some sort of "mental rotation in three-dimensional space," then the slope of the obtained functions indicates that the average rate at which these particular objects can be thus "rotated" is roughly 60° per second.

Of course the plotted reaction times necessarily include any times taken by the subjects to decide how to process the pictures in each presented pair as well as the time taken actually to carry out the process, once it was chosen. However, even for these highly practiced subjects, the reaction times were still linear and were no more than 20 percent lower in the "pure" blocks of presentations (in which the subjects knew both the axis and the direction of the required rotation in advance of each presentation) than in the "mixed" blocks (in which the axis of rotation was unpredictable). Tentatively, this suggests that 80 percent of a typical one of these reaction times may represent some such process as "mental rotation" itself, rather than a preliminary process of preparation or search. Nevertheless, in further research now underway, we are seeking clarification of this point and others.

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1. Mrs. Jih-Jie Chang of the Bell Telephone Laboratories generated the 180 perspective projections for us by means of the Bell Laboratories' Stromberg-Carlson 4020 microfilm recorder and the computer program for constructing such projections developed there by A. M. Noll. See, for example, A. M. Noll, *Computers Automation* **14**, 20 (1965).
2. We thank Mrs. Chang [see (*1*)]; and we also thank Dr. J. D. Elashoff for her suggestions concerning the statistical analyses. Assistance in the computer graphics was provided by the Bell Telephone Laboratories. Supported by NSF grant GS-2283 to R.N.S.

9 March 1970; revised 8 September 1970 ■

Neural Pathways Associated with Hypothalamically Elicited Attack Behavior in Cats

Abstract. *Small electrolytic lesions were made in cats through electrodes, which, when stimulated, elicited either quiet biting attack or affective paw strike attack upon rats. The Nauta method for impregnating degenerating axoplasm was used to reveal that degeneration resulting from lesions at quiet attack sites followed largely along the course of the medial forebrain bundle, while the degeneration after lesions of affective attack sites was concentrated more heavily in the periventricular system.*

Although it is now firmly established that the hypothalamus is intimately involved in the elaboration of aggressive behavior (*1*), very little is known about the neural pathways through which such behavior is mediated. In an attempt to trace out the circuits which may be associated with a cat's attack upon a rat we have employed neuroanatomic techniques in conjunction with stimulation experiments.

The development of silver stains capable of selectively impregnating degenerating axoplasm by Nauta (*2*) has dramatically increased the ability of neuroanatomists to determine the polarity of conduction and the areas of termination of finely myelinated and unmyelinated fiber systems. The first step in tracing out degeneration by this technique consists in destroying a small amount of neural tissue in a selected anatomic target area and then permitting the animal to survive for a

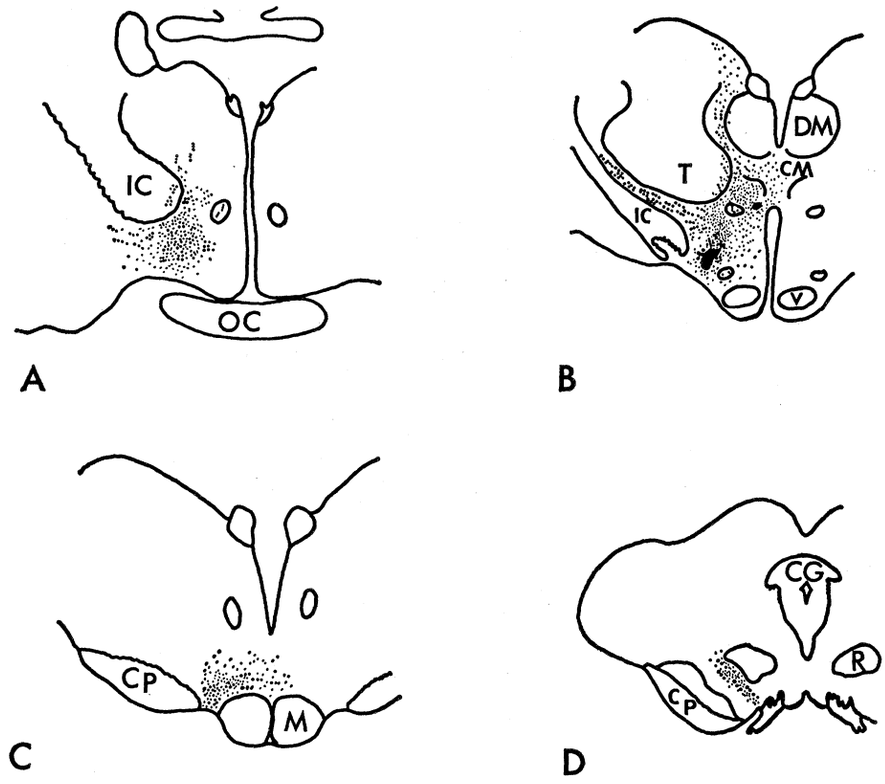

Fig. 1. Representative chart of degeneration after lesion of quiet biting attack site, plotted on frontal sections, cat brain 01130. (A) Most rostral section; (D) most caudal section. Abbreviations: *CG*, central gray; *CM*, nucleus centralis medius; *CP*, cerebral peduncle; *DM*, dorsomedial nucleus; *IC*, internal capsule; *M*, mammillary body; *OC*, optic chiasm; *R*, red nucleus; *T*, ventral nucleus of thalamus; *V*, ventromedial nucleus of hypothalamus.

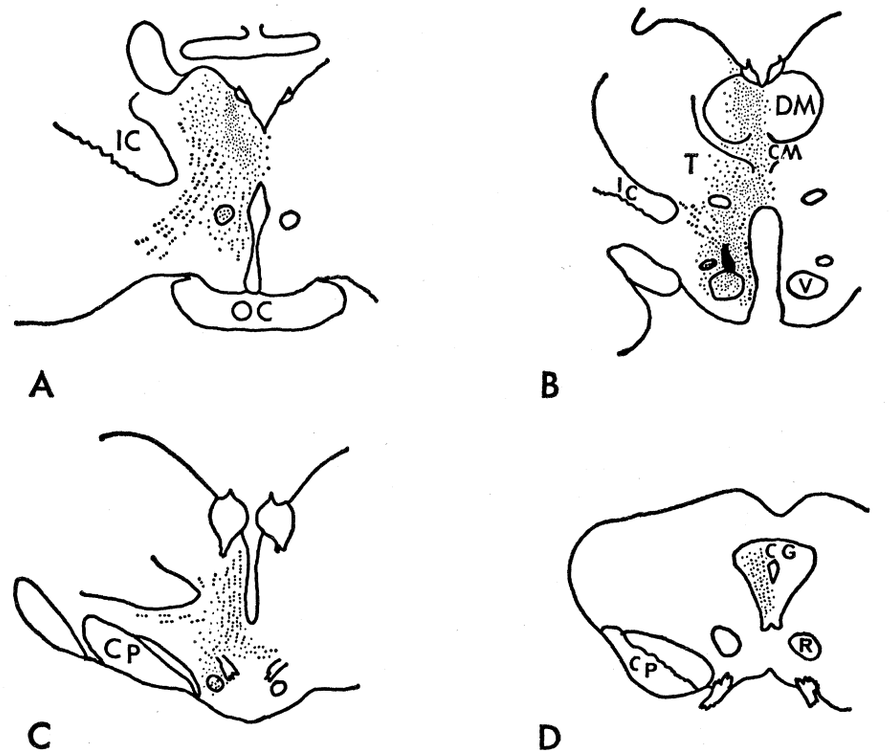

Fig. 2. Representative chart of degeneration after lesion of affective attack site, plotted on frontal sections, cat brain 03180. (A) Most rostral section; (D) most caudal section. See Fig. 1 legend for abbreviations.

time sufficient to allow the damaged axons to degenerate. We have utilized *behavioral* rather than anatomic criteria for determining the precise area to be destroyed.

Short pieces of wax-filled hypodermic tubing were cemented on the skull above the hypothalamus in seven cats during aseptic operations. Only cats that would not attack rats spontaneously were used in the study. Approximately 1 week after surgery each cat was placed in a large observation cage which contained a deeply anesthetized rat and a bowl of food. Small bipolar electrodes, made by tightly twisting two Teflon-insulated stainless steel wires together and coating them with a thin layer of epoxy resin (*3*), after being sterilized, were inserted at approximately 0.25-mm steps through the guides into the brain. The cat was stimulated at each step for up to 30 seconds with a train of 60-hertz biphasic square-wave pulses of 1.0 msec half-cycle duration, and its behavioral response was recorded. Five minutes elapsed between trials. When either a quiet biting attack or an affective attack on the rat was elicited upon stimulation (*4*), the electrode was temporarily held at that point with bone-wax, and at least five more trials were given to ascertain the stability of the attack.

In quiet biting attack the cat directly approached the rat and bit its neck and head repeatedly, usually killing it with the first bite. The food was ignored even when placed so that the cat had to pass over it to get to the rat (*5*). The cat showed few obvious signs of autonomic arousal other than pupillary dilatation and slight piloerection of the fur along the back and tail. During affective attack the cat struck the rat with its paws and then often bit it, although the bites were not aimed precisely. There was hissing, spitting, growling, retracted ears, pupillary dilatation, and very marked piloerection. Curiously, affective attack was less harmful to the rat than quiet attack.

Immediately after these trials, small electrolytic lesions (*6*) were made through the bipolar electrode, and the cat was then stimulated through this electrode with a current of up to two to three times the intensity at which attack was previously elicited (*7*). If attack could not be elicited at this higher intensity, the electrode was removed and the electrode guide cemented-over to prevent infection. If attack was still obtained, the lesion was

made larger in small steps until we could no longer elicit attack at high stimulation intensities. After attack was eliminated by the lesion, the cat no longer approached the rat but showed only a slight degree of alerting in response to stimulation. Our purpose was to make a small, well-circumscribed lesion that would eliminate as many fibers associated with attack as possible. The maximum diameter of our lesions varied from about 0.5 mm to 1.0 mm.

Seven to 14 days after lesions were made the cats were perfused under deep anesthesia with physiological saline and 10 percent formalin. The brains were sectioned on a freezing microtome, to a thickness of 26 μm and alternate sections were stained with either cresylecht violet or a modified Nauta stain for degenerating axoplasm and axon terminals (*8*).

Figures 1 to 3 show the degeneration resulting from lesions of quiet or affective attack sites in four cats. Lesions of quiet attack sites (Figs. 1. and 3A) produced degeneration mostly in the medial forebrain bundle which reciprocally interconnects the hypothalamus with the midbrain tegmentum and the basal olfactory and limbic structures of the forebrain. There is also degeneration in the midline nuclei of the thalamus, a region from which quiet biting attack can be elicited electrically (*9*), and in the stria medullaris, although the stria degeneration is probably due to damage caused by the electrode track rather than the lesion itself (*10*). In contrast, the degeneration after lesions of affective attack sites (Figs. 2 and 3B) is confined largely to the periventricular system, an association pathway (*11*) between the medial hypothalamus and the midbrain central gray. The projection from hypothalamic affective attack sites to the central gray substance is particularly interesting since affective attack marked by striking can be elicited by central gray stimulation (*12*), and lesions of the central gray have been found to block affective attack elicited by stimulation of the hypothalamus (*13*). Fibers associated with quiet biting attack, on the other hand, appear to descend primarily through the ventrolateral reticular formation of the brainstem (Fig. 1D). Hypothalamically elicited quiet attack can be facilitated by concurrent reticular stimulation (*14*).

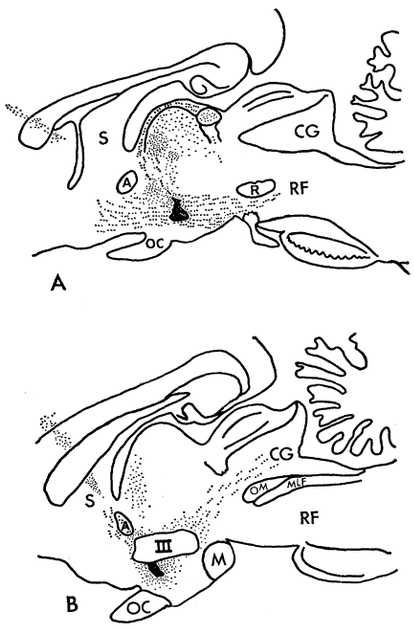

Fig. 3. Representative charts of degeneration plotted on sagittal sections. (A) After lesion of quiet biting attack site, cat brain 04030. (B) After lesion of affective attack site, cat brain 04020. Note that (B) is a more medial section than (A). Abbreviations: *A*, anterior commissure; *MLF*, medial longitudinal fasciculus; *OM*, oculomotor nucleus; *RF*, reticular formation; *S*, septum; *III*, third ventricle. See Fig. 1 legend for additional abbreviations.

Since there are many other functions besides attack behavior which are mediated by the hypothalamus, and since attack behavior can occur even when the hypothalamus is essentially isolated from the rest of the brain (*15*), it is obvious that not all the degenerated pathways are related to attack, nor have all the attack pathways been destroyed by these lesions. Nonetheless, some of the fiber systems destroyed are indeed associated with hypothalamically elicited attack. If the lesion did not include any "attack fibers" we would expect the attack to be obtained following the lesion, and in fact it was not, even when intensities two or three times greater than the previously effective values were employed. In further support of the involvement of the degenerated pathways in attack, others, as mentioned above, have reported that attack can be elicited by stimulation and blocked by lesions of some areas to which the degenerated fibers project. Furthermore, we believe that a *substantial proportion* of the degenerated fibers are involved in attack, since we found that as little as 0.5 mm separated a nonattack point from an attack point, indicating that even though attack can be elicited from many sites within the brain the pathways are discrete, in contrast, for example, to the pathways associated with pupillary dilatation which are diffusely spread throughout the neuropil (*16*). In addition, the size of the lesion sufficient to block attack was small, so that the number of irrelevant degenerated fibers was less than if the lesion were larger.

We believe our use of brain stimulation to determine the behavioral function of an area, together with anatomic techniques to trace out the associated pathways, has proved an effective means of correlating aggressive behavior with the anatomic structures which underlie it.

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2. W. J. H. Nauta, *Schweiz. Arch. Neurol. Psychiat.* **66**, 353 (1950); ——— and P. A. Gygax, *Stain Technol.* **21**, 91 (1954).
3. The maximum outside diameter of the bipolar electrode shaft was 250 μm. The tips were separated by approximately 50 μm.
4. Attack was defined as a bite or strike of the paw. Quiet attack was obtained in four cats and affective attack in three. Quiet attack sites were located in the lateral hypothalamus, while affective attack sites were usually found in the medial hypothalamus near the fornix.
5. R. R. Hutchinson and J. W. Renfrew [*J. Comp. Physiol. Psychol.* **61**, 360 (1966)] reported that quiet attack and eating were invariably elicited from the same points in the hypothalamus; however, we [H. Vanegas, A. Q. Siegel, C. C. Chi, J. P. Flynn, *Acta Cient. Venez.* **20**, 127 (1969)] have not found this to be so.
6. The lesions were made with a constant-current d-c lesion maker, which was set to deliver 0.5 ma for 30 seconds.
7. The peak-to-peak threshold intensity necessary to elicit attack prior to making a lesion was between 0.2 and 0.4 ma.
8. Two recently developed modifications of the original Nauta techniq[illegible] [R. P. Fink and L. Heimer, *Brain Res.* **4**, 369 (1967); R. P. Eager, *ibid.* **22**, 137 (1970)] are especially suited for impregnating degenerating presynaptic fibers and axon terminals. These were the principal methods employed in this study. A full discussion of the procedures used for selecting the best silver stain for each brain is in preparation.
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10. Degeneration resulting from passage of the electrode through a given region was minimized by use of a small-diameter electrode with a smooth shaft. In three cats, including both of those illustrated in Fig. 3, the electrode was inserted at an angle of 34° to the vertical plane so as not to penetrate the thalamus, while in the remaining four cats the electrode was inserted parallel to the vertical plane. Thus, different parts of the brain were penetrated in reaching the hypothalamus, and the degeneration produced by electrode track damage is controlled for by considering only the degeneration common to all the brains with lesions in the same area. For this reason it is probable that the degeneration in the medial thalamus shown in Fig. 2, as well as the stria medullaris degeneration illustrated

in Fig. 3A, is the result of passage of the electrode.
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17. Supported by NSF grant GB 19687 to C.C.C., and PHS grant 5-R01-MH08936 to J.P.F. We thank Fay Gomes and Mildred Groves for their skillful preparation of the brain sections.

14 September 1970

Aphrodisiac Effect of p-Chlorophenylalanine

Two recent reports by Whalen and Luttge (*1*) and by Zitrin *et al.* (*2*) dispute the view that a *p*-chlorophenylalanine (PCPA) is an aphrodisiac for male animals. Since the above authors refer repeatedly to one of our previous works (*3*) and since a negative conclusion on a drug possessing such a unique pharmacological action should be inferred with great care, we were prompted to offer the following comments.

Whalen and Luttge (*1*) deny that PCPA is an aphrodisiac for rats and cats and suggest that it "merely" alters the male's ability to adequately distinguish appropriate sexual partners. We are unaware of any definitions of an aphrodisiac more specific than those given by Webster's *New International Dictionary* (second edition): "that (as a drug or certain foods) which excites to venery" or by Dorland's *Illustrated Medical Dictionary*: "exciting the sexual impulse; any drug that arouses the sexual instinct." Whalen and Luttge's statement that PCPA and the combination of PCPA and pargyline are not aphrodisiac since they do not prolong or intensify male-female sexual interactions is therefore arbitrary. The only conclusion that can be drawn from their study is that PCPA does not enhance maximal performance. In fact, the seven rats used by these authors in their study were "known to be vigorous copulators"; without PCPA they exhibited an average of 7 ± 0.9 ejaculations during a single test. If one accepts the dictionaries' definitions of aphrodisiac, studying an aphrodisiac in "vigorous copulators" is no more logical than screening antidepressant drugs in normally happy subjects. Since Whalen and Luttge do not present an upper limit for the numbers of ejaculations, it is not certain whether this performance could possibly have been exceeded even with the help of drugs.

A similar criticism can be raised about the report of Zitrin *et al.* (*2*). In addition, before treatment all 12 male cats used in their study copulated with receptive females and 10 of them mounted normal and even anesthetized males. Before the experimentation, the cats were tested several times a week for a period of several weeks, in order to establish a stable base-line measure of behavior. It is possible that the repeated testings produced a Pavlovian conditioned sexual reflex so that the animals would mount not only females but also males or anesthetized animals, provided the stimulus animal was introduced to the alcoves through the same sliding window. A valuable insight to this problem would have been offered by the latency scores for the first mount or grip after the stimulus animals were introduced into the males' cages. Although the authors state that the general behavior failed to indicate any heightened sexual interest in the cats as a result of treatment, they give no quantitative values for parameters other than frequency of intromission. On the other hand, the fact that the cats did not mount a toy either before or after administration of PCPA indicates that PCPA did not merely alter the male's ability to adequately distinguish appropriate sexual partners (*1*). We have shown that PCPA and the combination of PCPA and pargyline increase the heterosexual copulatory performance of male rats when the experimental subjects, unlike the above studies, are chosen among sexually sluggish animals (*4–6*).

Moreover, the fact that the administration of pargyline alone completely suppresses the sexual behavior and that this is restored by PCPA (*5*) offers indirect evidence that PCPA has a true aphrodisiac effect, provided the males are not selected from animals with high levels of sexual activity. Finally, we believe that one need only witness the violent and persistent manner in which an adult male rat, treated with PCPA, struggles to mount a nonreceptive female to be convinced that the drug enhances sexual motivation.

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7 December 1970

Hemoglobin Polymorphism

Crawford (*1*) reported a hemoglobin polymorphism in a laboratory population of pigtail macaques (*Macaca nemestrina*) consisting of two common types of hemoglobins and three phenotypes, one similar to human A, one faster, and a third consisting of both components.

Similar results were found by Ishimoto *et al.* (*2*) who reported polymorphism in the pigtail macaques, but noted that the variants found were limited only to the Thailand subspecies. However, it appears that the very high frequency of the variants found by Crawford is anomalous, at least, judging from the findings of Nute and Stamatoyannopoulos (*3*) who failed to demonstrate such a polymorphism in their sample. The high frequency reported by Crawford (*1*) was probably due either to an unusual captive sample or the misclassification of several of the monkeys used in the study.

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