SENSITIZATION OF THE SPINAL CORD OF THE CAT TO PAIN-INDUCING STIMULI*

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SENSITIZATION of a functional unit of the central nervous system by partial injury or destruction is well known. Cannon and Haimovici in 1939 reported that motoneurones could be sensitized by partial "denervation." Cannon and Rosenblueth described the sensitization of both cholinergic and adrenergic elements in the autonomic system following injury to its neurones. Cannon then postulated a "law of denervation" for the efferent systems which required sensitization as the result of partial destruction. Drake and Stavraky then carried this concept into the afferent systems and showed that deafferentation caused systems to react more quickly and more intensely than did normal units. In their chronic cats, injection of either cholinergic drugs, camphor or metrazol produced convulsions which appeared earlier and more intensely in deafferented limbs than elsewhere.

Clinically, lowered threshold and increased sensitivity may result from direct sensitization of cells within a system. Injury to dorsal root ganglia is thought to cause pain in this way and trauma can so sensitize the cells of the cerebral cortex that epilepsy results from minor stimulation. Such cortical sensitization may follow destructive lesions and scar formation. It may be relieved in man by the removal of the scars. Chronic experimental epilepsy, produced by the application of alumina cream to the cerebral cortex in monkeys, must be the result of similar processes.

When peripheral nerves are damaged sensitization of the sensory system which mediates pain may result in hyperalgesia or causalgia. These painful states are most often unrelieved by the removal of the original source of the disorder at the site of initial injury. It has therefore been assumed that the initial injury has in some fashion sensitized the central nervous system. The concept of the neuron pool which effectively perpetuates the afferent input has been developed here.

The presence of hyperalgesia in cats as the result of injection of alumina cream into the spinal subarachnoid space may be considered as an example of chronic sensitization of an afferent complex within the central nervous system. It has been reported in detail elsewhere. The present paper is the result of subsequent investigations and will deal with the nature of this sensitization. A brief review of the development of the hyperalgesia as previously reported is here necessary.

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Nature of the Hyperalgesia. In the cats described in the previous papers hyperalgesia developed according to a fixed pattern which was similar in each animal. Following the injection of the colloidal substance into the dorsal spinal subarachnoid space, segmental skin areas became greatly sensitized to any form of cutaneous stimulus. Light touch or pin-prick, which produced only mild responses if applied to normal skin areas, caused extreme reactions of displeasure in the affected regions. Blowing on the hair, a slight touch, or even the tension caused by the animal's moving would produce withdrawal, crying-out and, sometimes, resistance. The animals became sedentary and dirty, since they could not clean the hypersensitized fur. But their non-affected regions were clean and they remained friendly and sought petting in the normal areas. A causalgia-like syndrome was thus defined.

Rate of Development. Following injection, the hypersensitivity to touch and pain first appeared, in some animals, on the 5th postoperative day. In others, symptoms were not noted until the 3rd week. The amount of substance injected was thought to have direct relation to the rate of development, although no quantitative experiments were carried out. Following the onset, the hyperalgesia usually became intensified over a period of several weeks. Once fully established it was permanent for as long as 3 years.

Extent of Hyperalgesia. The hyperirritability to sensory stimuli appeared first just below or at the level of the injection. It then spread bilaterally during a period of about 2 weeks, becoming equally intense through all levels below the site of the injection and for one or two segments above it. This occurred whether the injection was made low in the lumbar region or high in the cervical; thus a varying amount of skin area might be involved, increasing as the injections were made higher in the cord. It was thought that this must indicate a local action of the substance at the level of injection rather than action over a long distance of cord, for, in the latter instance, the diffusion should be equal in either direction from the site of injection. No actual determination of the diffusion of aluminum ions has been made, however.

METHOD

The details of the injection of alumina cream have have been given previously, as have the method of examination and the clinical status of the animals.\(^7\)\(^8\) In the present study as in the previous ones the colloidal alumina cream has been made for us by Dr. Lenore Kopeloff according to her original method.\(^10\) In the present study the substance was injected into the cervical, rather than lumbar region; either into the subarachnoid space (3 cats) or directly into the lateral column of the cord of one side (5 cats). Findings have been compared with those of the earlier series.

DATA

The findings in all 8 cats are consistent although different secondary procedures often altered the course of the disorder. The following brief
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clinical history of one animal describes the development of postoperative hyperalgesia.

This was a mature male cat weighing 2.9 kg. at onset of the procedure and 3.7 kg. 1½ years later. It was of reasonably tame and friendly disposition and had short hair which facilitated sensory examination (Series No. 35). On Aug. 1, 1949, under nembutal anesthesia, a small drop of colloidal alumina cream was injected into the right lateral cervical cord substance at a midcervical level.

On the 2nd day the animal had eaten but appeared rather sedentary. It stood and walked without apparent difficulty but occasionally the right hind leg showed some postural distortion which might have been proprioceptive. On the 7th day no postural deficit remained and none occurred thereafter. On this date hyperalgesia to pin-prick first appeared. It was reported as moderate and extended from the region of the neck incision down. On the right side, at the level of the injection it was markedly more intense than elsewhere. By the 11th day the hyperalgesia had increased. It was then more marked in cervical and thoracic regions than "lower down." It was bilaterally equal. This status was still present on the 21st day, but by the 25th day extreme hyperirritability was noted throughout all levels below the incision. By the end of the 6th week a state had developed that persisted unchanged for the subsequent 1½ years until the animal was killed.

At the end of the 3rd month a protocol note reads as follows: "The sensory abnormality in this animal is now very marked and easily demonstrated. The fur below the cervical segments is rough and matted. About the head and neck it is smooth and clean. The animal moves little, preferring to remain crouched in the middle of its cage where it receives the least sensory stimuli. To light touch or pain stimuli there is a prompt protest as well as a reflex jerk. Hyperirritability is extreme. It extends throughout the whole body. The right foreleg is more affected than the left. It jerks to the slightest stimulus as do both hind legs, whereas the left foreleg only occasionally shows this type of response to stimuli on the left shoulder or to light touch applied to the dorsum of the foot."

One year later: "This animal shows exactly the same characteristics as have been described many times before. It tends to remain immobile with the legs folded beneath its body and the tail wound to the side. . . . The line of poorly cleaned fur is definite on both sides."

The involvement in this animal was repeatedly found to be at the cervical level and somewhat higher on the right than on the left side. In no cats, following injection into either the subarachnoid space or within the cord substance, was a distinct line of demarcation ever demonstrable between normal and hyperirritable skin regions. Rather the border appeared to fluctuate slightly both in degree of hyperirritability and in level. In this respect also, therefore, their condition resembled the causalgic states in man.

Injection of alumina cream into the lateral cervical cord substance in 4 other animals produced like syndromes and additional evidence as to the nature of the hyperirritability. In these later cats the injection was smaller and more sharply localized, as shown by subsequent histological section. In each cat the development of intense, bilateral hyperalgesia oc-
curred which included all spinal segments caudal to the injection and one or two in a rostral direction. The march of symptoms was the same in each case. All of these cervically injected animals showed a brief transient motor disability in the ipsilateral hind leg. Following this, no motor defect was observed. But there was always a marked increase in deep reflexes which caused at times a stammering, clonic type of movement during progression, especially when the animal was forced to move quickly. Skill in fine movements was unaltered.

Various attempts were made to modify the hyperalgesia and hyperreflexia in these cervical animals. This was done either by drugs or by cord section subsequent to the full development of hyperirritability. The results are here summarized. In addition to clinical observation of the behavior of the cats and their reactions to stimuli, the hyperirritability was demonstrated electromyographically in each animal. Under light dial anesthesia, needle electrodes were inserted bilaterally into various symmetrical muscle groups up and down the spinal musculature and in the extremities. A brief electrical stimulus or a mechanical pinch would then cause a characteristic muscle twitch which was recorded on a Grass 8-channel machine. Under these conditions it was consistently easy to demonstrate that the threshold for muscle twitch was lower and the response greater in the hyperirritable than in the normal regions.

As reported earlier, decerebration of a cat with sensitized lumbar and sacral regions was followed by markedly greater hyperreflexia in the hyperirritable hind legs than in the previously normal forelegs. Similar results were obtained following acute cord transection in the cervical region after sensitization of the lumbar region had become chronic.

Two cats were made hyperalgesic from the high cervical regions down. Subsequent cord transections were made at lower thoracic levels and the animals were kept alive for 5 and 7 days respectively. There was no doubt but that the reflex status below the cord transection was one of unusual and extreme hyperirritability. If the cord of a normal cat is transected at this level, deep reflexes below the transection may disappear or become greatly diminished and will remain so for several days. The reflex status then shows a gradually increasing irritability until the chronic state, usually during the 2nd postoperative week, when marked hyperreflexia appears. These same changes are those that develop, although much more slowly, in spinal man. In the hyperalgesic cats, no stage of hyporeflexia appeared and the extreme hyperirritability of skin areas persisted as shown by twitching responses to slight stimuli, although of course no subjective response was possible. Knee jerks were 4 plus from the time of cord transection. These experiments demonstrated that the state of hyperirritability was not dependent on the presence of the original site of the injection.

The effects of various drugs were tried many times without any pronounced results. These experiments were carried out in collaboration with Dr. Frederic P. Haugen, Chief of the Department of Anesthesiology at the
University of Oregon Medical School, who directed the injections and the amounts of drug used. Since we were not sure of the effective dosage, the size was increased in a series of animals until profound and characteristic changes were induced. In the case of morphine, respirations diminished and the animals finally became totally unresponsive. Procaine was pushed in one instance until a convulsion resulted. In both cases the difference between normal and hyperirritable skin areas remained.

Morphine, procaine and myanesin were each given several trials, both intravenously and intraperitoneally, in unanesthetized animals. There was never any effect on hyperirritability as demonstrated by the behavior of the cat. When dial anesthesia was given the responses to painful stimuli became less and less as the anesthesia deepened. During this interval those areas that had been first and most intensely affected remained more hyperirritable than did those later affected. That is, in the cervically injected animals, deepening anesthesia reduced the area of hyperirritability to the cervical and upper thoracic areas where it had first appeared. Under light dial anesthesia the intensity of the response to painful stimuli was diminished slightly as the result of injection of morphine or procaine. Myanesin never produced any such effect.

Additional information as to the type of change produced within the nervous system was obtained from histological sections. When the substance was injected into the cord the site and extent of the area injected was verified by serial sections stained by the Nissl method. Marchi and Nissl stains of sections from above and below the level of the injection gave added information. Rostral to the lumbar subarachnoid injections there was some degeneration of the axons lying in the posterior and posterolateral columns. It was spotty and slight and was never seen as any large destruction of any tract. It is notable that it appeared in posterior columns although no lasting defect in proprioception could ever be shown. It is notable also that the degeneration in ventral and ventrolateral columns was less. Since the Marchi method stains only myelinated fibers, no information as to unmyelinated fibers is available. Weigert preparations of sections made on a number of these cats with older lesions were unproductive; the degeneration is probably too scattered and fine to show by this method. Silver staining, not yet available, might give more definite results.

**DISCUSSION**

Examination of the experimental hyperalgesia produced by the discrete injection of alumina cream into the cervical cord substance in the cat has confirmed the previous findings resulting from injection of larger amounts into the spinal subarachnoid space at lumbar levels. It can now be concluded that the injury is directly upon the axons of the afferent tracts transmitting pain and that this change in some way permanently sensitzes the afferent system to which these axons belong. This deduction is based on the nature of the changes, which are to be compared with those resulting from pe-
ripheral nerve injury, and upon the extent of the involvement throughout
the segments caudal to the injection.

Changes confined to the very sensitive dorsal nerve roots or their gang-
lion cells or to the cell groups within the cord at the level of injection are not
possible, as the extent of hyperalgesia would then be limited also to this
level. If the nerve roots were the source of the irritation, moreover, a sharper
line of demarcation between affected and non-affected areas might be ex-
pected.

The inference from physiological observations is that the fine myelinated
and the non-myelinated fibers are those that are altered, since it is these
that are known to transmit pain in man, and that the thicker motor and
proprioceptive fibers, which are more heavily myelinated, have been more
resistant to the action of the aluminum. This is borne out by the histological
findings in the cords, which show degeneration of scattered fine fibers rather
than of compact tracts. In sections stained by the Marchi method this de-
generation lies chiefly in dorsal and dorsolateral tracts which is also con-
sistent with what is known of the afferent fibers in the cord of the cat. In
this animal, bilateral ventral cordotomy has no effect on pain perception,
whereas bilateral section of dorsal quadrants consistently produces hyp-
algesia. The tracts transmitting pain therefore lie in the dorsal quadrants
of the cat’s cord.

In the cat, furthermore, it has been shown that transmission of pain in
the cord substance is bilateral. Ranson and von Hess in 1915 first demon-
strated that hemisection of the cord in the normal cat had no effect on pain
sensation. This observation has been confirmed by the writer by hemise-
ctions performed on both normal and hyperalgesic cats. The fact that, in the
present series, hyperalgesia first appeared ipsilateral to the injection and at
that level, spreading later to both sides and caudally, must mean that there
is some lamination or arrangement of fibers that makes those that are
first affected consistently more vulnerable than those that are later involved.

The nature of the action on the axons might be one of several. Anatomically
the tracts might be totally or partially damaged. The fibers might be
destroyed or merely altered. All or part of the system might be involved.
Analogous hyperalgesia occurs when peripheral nerves are damaged and the
evidence there seems to be that pain follows when nerves are stretched or
crushed rather than cleanly severed. The extensive literature on this sub-
ject has been discussed in detail by Sunderland and Kelly.

In the partially destroyed system the remaining axons may function in
one of several ways. At the level of the injury, axons may be producing a
constant stimulus which results in overreaction when there are additional
stimuli from the environment. Or the hyperalgesia may be caused by a
lowered threshold at the site of injury. The state of hyperirritability herein
described, however, can not be the result of either of these possibilities alone
since hyperreflexia remained in the sacral segments of a cord previously
sensitized by a cervical injection, after that area of injury had been discon-
connected by complete cord transection at an intervening thoracic level. Potentiation of the entire segmental nervous system innervating the pain tracts of the affected areas must therefore have occurred.

There is plenty of evidence that such potentiation may occur. Injury to axons always produces retrograde changes in the original cell bodies which are always more marked histologically the nearer the injury is to the cell of origin. Sunderland and Kelly\textsuperscript{14} have shown, in studying a series of peripheral nerve injuries in man, that “the higher on the pathway the level of the lesion is the more likely causalgia is to ensue.” They state that “The clinical evidence suggests that the painful sequelae of nerve injuries are the effect of damage to the central nervous system by retrograde and transneural changes. A center of abnormal spontaneous activity is thereby set up in the cord which acts as a focal point for the dissemination of spreading disturbances involving wider and wider areas of the cord.” There are no data at the present time that interfere with the application of this concept to the hyperirritability which is here under discussion.

The concepts of Wolff\textsuperscript{6} and of Livingston,\textsuperscript{11} which provide potentiation within a reverberating circuit or a neuron pool to explain referred pain and causalgia, are in accord with the present data also, although the present data require potentiation in the cord alone and not at higher levels. No evidence is available, however, to prove that potentiation may not also exist elsewhere.

Another phase of the hyperirritability deserves comment, namely that a painful state has been induced by alteration in the spinal cord. Clinically, in man, pain as the result of cord lesions is unknown although dorsal roots and ganglia are excessively sensitive to injury, from which pain always results. However, Sweet and his associates\textsuperscript{15} have reported that pain can be experienced by unanesthetized man as the result of stimulation of the exposed cord. They produced it from stimulation of both dorsal and ventral quadrants, although its character differed in the two places. The threshold for pain from stimulation of the cord was, however, many times higher than that for stimulation of dorsal nerve roots and the character of the pain from cord stimulation was much more bearable than that from stimulation of the dorsal roots.

It should be noted here that, as far as could be observed in animals, the pain that appeared as the result of the present experiments was very like the causalgia of man. It was of marked intensity; its segmental limitations were indefinite; it could be produced by very slight stimuli which ordinarily were those felt as touch rather than pain; and it did not influence the character or psychological behavior of the subjects except when present. These animals remained peaceful and friendly, as they had been previous to operation, except when receiving disagreeable stimuli.

Analyses may be drawn between the hyperalgesic state and the experimental epilepsy which can also be produced by alumina cream.\textsuperscript{10} It has been reported\textsuperscript{11} that the histological change produced in the cortical tissue by
alumina cream is "essentially that of a chronic progressive meningocortical cicatrix," but that a similar type of lesion was produced by control preparations, using substances other than aluminum, which failed to induce convulsive seizure. Thus, no histological change that is pathognomonic for the aluminum substance, which is the only substance producing this irritation, has yet been found. But, if the changes in the cerebral cortex are the result of action upon the small myelinated or non-myelinated fibers, as they appear to be in the cord, and if the other substances can be shown to produce no such changes, the difference in resulting symptomatology may be explained. Since changes in small fibers are most difficult to detect it is very possible that their specific degeneration in the cortex in relation to epilepsy has been missed. The concept of a fine-fiber meshwork which may be altered by injury within the cortex is entirely possible in relation to what is known about the clinical manifestations of epilepsy. The potentiation of its cells of origin may underlie its abnormal activity.

In both its cortical and cord effects colloidal alumina cream might then be unique in producing by chemical means a partial destruction of those anatomical systems composed of fine and little-myelinated fibers and a resultant permanent hyperirritability. If this is so, then the substance should also be effective on the autonomic systems and in the peripheral nerves and in both places should produce afferent hyperirritability which might resemble clinical states in man.

CONCLUSIONS

1. The production of permanent hyperalgesia following injection of alumina cream at the cervical levels of the cord in the cat has been established.

2. This hyperalgesia involves all areas caudal to the level of injection and one to two segments rostrally.

3. There is no distinct level between normal and hyperalgesic skin and there is some fluctuation in degree of hyperalgesia. In both these attributes and in its severity this hyperalgesia in cats resembles causalgia in man.

4. The hyperalgesia cannot be attributed to potentiation of parts of the central nervous system lying rostral to the lesion since it persists following decerebration and following section of the cord both above and below the level of injection.

5. The hyperalgesia must therefore be caused by potentiation of neurons remaining active within the partially destroyed segmental system of the cord. In this respect it resembles the conditions in man which may follow injuries to peripheral nerves.

REFERENCES


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