FUNCTIONAL AND STRUCTURAL CHANGES IN THE MONKEY’S BRAIN DURING AND AFTER CONCUSSION*

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The present study was undertaken to check in a primate the functional alterations of simple concussion found in the cat and the histologic alterations demonstrated in the guinea pig. Little previous use has been made of monkeys to study functional aspects of concussion and it would seem that the present histologic results are the first obtained after simple concussion. It is unlikely that autopsy material will ever be available after simple concussion in man but the findings probably would not differ significantly from those in the monkey.

Denny-Brown and Russell employed monkeys, but most of their experiments were performed on cats. So far as their observations went, concussion and subconcussion were the same in the two species. Their protocols of four monkeys show that subconcussive respiratory and blood pressure alterations (with or without section of vagus nerves) were irregular. The concussive phenomena that they observed (with vagus nerves cut) were transitory loss of the corneal reflex, cessation of respiration and steep rise of blood pressure with a gradual decline within about 5 minutes. Concussion was characterized as a condition in which brain-stem centers are inert to reflex activation although they themselves may be in a state of stimulation. Denny-Brown and Russell had the opportunity to observe an intact unanesthetized monkey which was rendered unconscious in the course of an experiment with a model bomb shelter. Percussion injury sufficient to stun the animal abolished the corneal reflex although a lesser injury did not.

Experimentation on cats formed the chief basis for the conclusions of Walker, Kollros and Case, but some monkeys were used and presumably with similar results. They believe that the physiologic basis of concussion consists of depolarization of many nerve cell bodies within the central nervous system caused by the shaking up or vibration of the brain as a result of trauma, and that widespread central and peripheral excitation ensues as axons are fired by this electrical breakdown of the cell membranes. The authors enumerated tetanic phenomena, respiratory, blood pressure, heart rate and spinal reflex alterations and electrical disturbances as evidence for the validity of their theory.

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Shelden, Pudenz and Restarski\textsuperscript{4} have studied and demonstrated, by high-
speed motion picture photography, brain movements during subconcussive
and concussive blows to various parts of the monkey's head. They observed
the brain through very large apertures covered by a lucite calvarium.\textsuperscript{5} Pub-
lication of their most interesting studies on concussion is awaited.

Jakob\textsuperscript{3} attempted to investigate histologic changes following concussion
in three monkeys. Rabbits formed the bulk of his material. Concussions of
doubtful nature were produced in the monkeys by multiple blows. Infection
and malnutrition in the animals restrained the author from reporting any
observations except some Marchi degeneration.

METHODS AND MATERIAL

Physiologic studies were conducted in acute experiments on 7 rhesus monkeys lightly
anesthetized with chloralosane. Only mild concussion could occasionally be produced by
means of the pendulum or the hydraulic apparatus previously used on cats. Force applied
by either method sufficient to kill a cat would not affect a monkey. Rather than add weight
to the pendulum and incur the risk of fracturing the skull, the piston of the hydraulic ap-
paratus was increased in diameter and the falling weight was made heavier. In this way, a
force of sufficient magnitude to produce concussion in a monkey could be transmitted to its
brain. During the concussion experiment, the state of respiration, corneal reflex, spontaneous
motor activity and threshold of stimulus required to elicit appropriate responses of the motor
cortex, hypothalamus or facial nucleus were followed and recorded. Adequate recovery
intervals were allowed between blows in the same animal. Placement and fixation of electrodes
in the brain, stimulation and other details were like those described in concussion experi-
ments in the cat.\textsuperscript{3}

Three monkeys that had suffered concussion and one control supplied material for
the histologic study. One monkey, No. 6, was from the functional alteration series. It was
perfused with 10 per cent formalin (after washing out blood with 1 per cent NaCl solution)
at the termination of the experiment. A second, No. 9, was given a light concussion with the
hydraulic apparatus and sacrificed 6 days later. In the third, No. 11, severe concussion was
produced by striking with a hammer a Wood's metal life-cast attached to the intact head;
this specimen was sacrificed after 8 days. Monkeys 9, 11, and the control, No. 10, were given
anesthetic doses of nembutal and perfused with 10 per cent formalin (after washing out the
blood with 1 per cent NaCl solution).

The brains and spinal cords were carefully removed and the brain stems cut away from
the forward parts at the level of the superior colliculus. Each brain stem was placed in 10
per cent formalin for 36 hours; the cerebrum, divided in the midsagittal plane, was placed in
formalin for 5 to 7 days. The several pieces of the brain were then embedded in low viscosity
nitrocellulose and sectioned at 20\textmu and 40\textmu. The stem was cut serially in the transverse plane.
Groups of frontal sections were taken at five levels through the hemispheres. The first three
segments of the spinal cord were sectioned serially in the frontal plane and horizontal serial
sections of the upper part of C4 were prepared. Staining was by the buffered thionin tech-
nique (pH 4.3 and 4.9), as in previous studies of concussion changes in the guinea pig.\textsuperscript{7}

PHYSIOLOGIC RESULTS

\textit{Monkey 1}. One bipolar electrode was placed in the face area of the motor
cortex (response: contraction of labial musculature) and another in the
facial nucleus (response: contraction of labial musculature and eyelid clo-
sure). The pendulum apparatus was used. The first three blows were struck
on the temporo-parietal region of the skull, corresponding to the area struck
in the experiments with cats. The fourth blow was struck on the external occipital protuberance.

The first blow was strong enough to have produced moderate to severe concussion in the cat. No effect was obtained. The second blow would have produced severe and probably fatal concussion in the cat. A very light concussion was obtained. The corneal reflex was abolished for 25 seconds, respiration paused for 5 seconds, the pupils were dilated and the eyelids opened for 25 seconds. No changes in thresholds were effected. A linear fracture of the skull occurred. The third blow was of the same magnitude as the second. A light to moderate concussion was produced. The corneal reflex was out for 30 seconds; respiration was not interrupted. The threshold of the motor cortex rose from a control value of 2.5 volts to a concussional value of 5.0 volts, with recovery in 15 minutes. The facial nucleus threshold for the labial musculature rose from a control value of 0.9 volt to a concussional value of 1.0 volt. That for eyelid closure rose from 1.4 volts to 1.6 volts. Facial nucleus thresholds recovered in 5 minutes. A circular depressed fracture of the skull occurred. The fourth blow was of the same magnitude as the two preceding. A very light concussion was produced. The corneal reflex was out for 5 seconds and respiration was interrupted for 5 seconds. No change took place in the thresholds. A linear fracture resulted.

Monkey 2. No concussion was produced. The animal was used for another purpose.

Monkey 3. A bipolar electrode was placed in the facial nucleus (response: contraction of the inferior facial musculature). The hydraulic apparatus which had been developed previously for cat experiments was used for this monkey. The cannula of the apparatus was in the parietal bone in a position similar to that used in the cat experiments.

Six blows were delivered. They ranged in intensity from one that would have administered light concussion in the cat to the most severe possible with the apparatus. The last three blows each would have killed a cat. No concussion resulted in the monkey. The more severe blows resulted in short interruption of respiration, blinking of the eyelids, quivering of the trunk and a slight startle.

Monkey 4. A bipolar electrode was placed in the facial nucleus (response: contraction of the facial musculature). The hydraulic apparatus was used. The cannula was placed in the parietal bone.

Eleven blows were delivered. The first seven ranged in intensity from one that would have produced a light concussion in the cat to one almost as severe as was possible to obtain with the apparatus. No concussion occurred in any of these seven blows. The heavier blows caused a startle response and eyelid opening. The heaviest caused, in addition, a respiratory pause for 5 seconds. The four remaining blows each would have produced death in cats. One of them had no effect on the monkey, one caused very light concussion and two produced moderate concussion. The threshold was not affected.
CONCUSSION IN MONKEY

**Monkey 5.** A bipolar electrode was placed in the hypothalamus (response: pupillary dilatation). The same hydraulic apparatus was used.

The first four blows ranged in intensity from one that would have produced a moderate concussion in a cat to one that would have proved fatal. No concussion occurred in the monkey. The fifth blow did produce a moderate concussion. The corneal reflex was abolished for 15 seconds and respiration ceased for 15 seconds. The threshold rose from a control value of 1.4 volts to a concussional value of 1.8 volts. Recovery occurred in 2 minutes. The sixth and seventh blows produced no concussion. The eighth blow produced a moderate concussion. The corneal reflex was out for 65 seconds and respiration ceased for 10 seconds. No alteration in threshold was observed. Any one of the last four blows would have proved fatal in the case of the cat.

At this stage an hydraulic apparatus with a piston greater in diameter was devised. Subsequently, as noted in the following protocols, more weight was added to the disc that dropped onto the piston. Thus, we obtained an apparatus capable of delivering such force that even severe concussions could be produced without calling upon the maximum output of the apparatus. This meant hitherto unavailable controllability of concussions.

**Monkey 6.** A bipolar electrode was placed in the facial nucleus (response: eyelid closure). The remodeled hydraulic apparatus was used and the cannula was in the parietal bone.

The first five blows produced no concussion and only a slight startle response. The force applied was increased successively by closing by degrees the needle escape valve in the hydraulic system. The sixth blow was more severe than the preceding ones and produced a moderate concussion. The corneal reflex was abolished for 20 seconds but respiration was not affected. The pupils dilated and the eyelids opened. The threshold to stimulation rose from a control value of 1.8 volts to a concussional value of 3.0 volts; there was no recovery in 10 minutes. Blow seven was more severe than number six and it produced a moderate concussion. The corneal reflex was out for 25 seconds, respiration ceased for 25 seconds, the pupils dilated and the eyelids opened. The threshold to stimulation rose from a control value of 3.0 volts to a concussional value of 3.5 volts and there was recovery in approximately 10 minutes.

At this point in the experiment, additional weight was added to the disc that dropped upon the piston. The eighth blow was more severe than number seven. A moderate to severe concussion was induced. The corneal reflex was abolished for 75 seconds and respiration ceased for 25 seconds. The pupils dilated. The threshold rose from a control value of 3.0 volts to a concussional value of 3.5 volts. There was no recovery in 22 minutes. The ninth blow was one of the same magnitude as the eighth, resulting in a moderate concussion. The corneal reflex was out for 25 seconds and respiration ceased for 60 seconds. The pupils dilated. There was no increase in the threshold to stimulation. The tenth blow was approximately of the same mag-
ntitude as number seven. It gave a moderate concussion. The corneal reflex was out for 20 seconds, as was respiration. There was no increase in threshold to stimulation. The eleventh blow was the most severe of all, more weight having been added to the disc. A moderate concussion was produced. The corneal reflex was out for 25 seconds and respiration ceased for 35 seconds. No threshold changes occurred.

In all of these concussions, a startle or a struggle was observed upon delivery of the blow. Stimulation in the facial nucleus, besides eliciting the primary response of lid closure, also evoked a secondary struggle response. The threshold for this latter response showed greater elevation and slower recovery than that for the eyelid closure response.

**Monkey 7.** A bipolar electrode was placed in the facial nucleus (primary response: contraction of the facial musculature; secondary response: contraction of the abdominal musculature). The same hydraulic apparatus that was used in the preceding experiment was employed, but the weight of the disc that was dropped upon the piston was substantially increased.

The first blow produced a moderate concussion. The corneal reflex was abolished, although the time during which it was out was undetermined. Respiration ceased for 10 seconds. The threshold for the facial musculature response rose from a control value of 0.9 volt to a concussional value of 1.0 volt. The threshold for the abdominal musculature response rose from a control value of 1.0 volt to a concussional value of 2.0 volts. We were unable to determine the recovery time because a secondary cessation of respiration intervened. Artificial respiration was successfully applied for a short time, following which the experiment was terminated.

**Monkey 8.** A bipolar electrode was placed in the forelimb area of the motor cortex (response: forelimb movement). The same hydraulic system was used as in the previous experiment, with the cannula in the left parietal bone.

The first blow produced a light concussion. The corneal reflex was out for 15 seconds and respiration ceased for 10 seconds. The threshold rose from a control value of 5.0 volts to a concussional value of 6.0 volts. Recovery occurred in 13 minutes. The second blow was stronger than the first and produced a light to moderate concussion. A startle was noted at the instant of the blow. The corneal reflex was abolished for 20 seconds and respiration ceased for 7 seconds. The threshold to stimulation rose from a control value of 5.0 volts to a concussional value of 7.0 volts. Recovery took place in 31 minutes. A third blow was stronger than the second and produced a severe concussion. A startle occurred and the pupils dilated. The corneal reflex was abolished for a prolonged period of time and respiration ceased. The threshold to stimulation rose from a control value of 5.0 volts to a concussional value of 20 volts. Recovery of the corneal reflex and the threshold to stimulation occurred but was delayed. Artificial respiration was begun one minute after the blow and was successful. Ten seconds after the blow, the animal
slowly became tense and quivered. This general spasm gradually subsided over a 30-second interval.

HISTOLOGIC RESULTS

The most marked histologic changes were observed in the brain of Monkey 11, which was the animal struck upon a Wood's metal life-cast affixed to the calvarium with scalp intact. Four blows were struck with the following effects: blow 1, corneal reflex was not affected, respiration paused for 5 seconds; blow 2, corneal reflex was abolished 60 seconds, respiration ceased for 15 seconds; blow 3, corneal reflex and respiration both were abolished for 30 seconds; blow 4, corneal reflex was abolished for 5 seconds, respiration ceased for 20 seconds. Sufficient interval for complete recovery was allowed between blows. The animal was sacrificed 8 days later.

Throughout the brain stem much evidence of cytologic alteration was observed, though not in all of the cell groups. None of the primary motor nuclei exhibited damage. The changes appeared to be very largely confined to interneuron systems. Both large and small nerve cells were affected, the former most strikingly. Large neurons of the red nucleus, the pontile reticular formation, vestibular nuclei, superior olivary nuclei and the lateral reticular nuclei showed chromatolysis. Some of these cells were so completely destroyed that their remnants could be observed only by very careful study with a high-power lens. Many contained no Nissl bodies. In the upper cervical segments of the spinal cord, damage was confined to small and medium-sized nerve cells, especially those of the posterior grey columns.

It is impossible to estimate accurately the proportion of neurons affected by concussion. Ten per cent of those in the reticular formation is perhaps a reasonable guess for this one specimen. The amount of damage was less in this monkey than in some of the more severe concussions in guinea pigs.

In Monkey 9, light concussion was produced with the hydraulic apparatus. Aseptic technique was employed. The first blow did not affect the corneal reflex and caused a respiratory pause of only 8 seconds; upon the second blow, the corneal reflex was unelicitable for 12 seconds and respiration ceased for 10 seconds.

Histologic changes were observed, and their distribution in the brain stem was similar to that of No. 11. Structural alterations were slight and few cells were in a state of marked chromatolysis. There seemed to be nearly as many of the smaller interneurons of the brain stem affected as in the monkey that was struck with a hammer. Lower motor neurons of the brain stem were not affected. However, in the upper cervical spinal cord a few anterior horn cells showed mild central chromatolysis unlike that usually observed after concussion. These cells occurred in one thin linear column in the ventrolateral portion of the grey matter of one side and were not found elsewhere; most were found in a single 40μ section.
Monkey 6 was one that received many blows with the hydraulic system in the course of an experiment on functional alterations. This animal was perfused at the conclusion of the experiment. It provided material for the study of changes immediately after concussion. Some large neurons, especially those of Deiter's nucleus and the red nucleus, appeared to have suffered change. Comparison with the control specimen, No. 10, gave indication that the Nissl bodies had been fragmented and their pattern disorganized. The condition was not nearly as well defined, however, as in the guinea pigs in which perfusion with 10 per cent formalin was carried out immediately upon striking a blow.

Parts of the brain rostral to the mesencephalon showed less marked alterations after concussion. Eight days after concussion, in Monkey 11, changes were clearly observed only in the large motor cells of the cerebral cortex. These large pyramidal cells appeared shrunken, hyperchromatic and showed disturbances of the Nissl-body pattern. None of them was chromatolyzed. The changes are illustrated in Fig. 3.

The monkey that received two light blows with the hydraulic apparatus and was sacrificed six days later showed similar changes in the pyramidal cells of the motor cortex. These differed distinctly from the cells of the same region of the control animal and in the animal that was sacrificed at the conclusion of an acute experiment.

We were unable to observe structural changes in the cortex of the cerebellum. The various portions of the thalamus appeared to be little, if any, involved in structural alterations. The basal ganglia of the cerebrum and the cell groups of the hippocampus seemed to be normal. It is quite possible that more extensive investigation of structural changes in monkeys receiving blows of greater severity would reveal losses and damage which these few experiments failed to do. Nevertheless, it is clear that a differential effect like that in the guinea pig took place with damage of certain neurons, especially in the brain stem, after adequate force was applied to the brain of the monkey.

In none of our sections did we find even slight interstitial hemorrhages. There was no indication of any reaction about walls of blood vessels in the brains of monkeys that had suffered concussion. No glial reactions could be identified. Nerve fiber tracts showed no degenerative phenomena. The swelling of myelin sheaths seen in brains of guinea pigs after severe concussion was not observed in the monkey. In short, cytologic alterations were ascribable to uncomplicated concussion of the brain.

DISCUSSION

The present physiological experiments in rhesus monkeys demonstrate a differential change upon concussion of the brain similar to that reported in the cat. Function of the motor cortex of the cerebrum and of other supranuclear motor regions was more adversely affected than was function of cranial motor nuclei. The latter usually exhibited slight or no elevation in
threshold of stimulation immediately after a concussive blow had been struck. In five instances in which the corneal reflex was abolished long enough to make trustworthy observations, the threshold of the facial motor nucleus for eyelid closure was unchanged in concussion, although the corneal reflex itself was absent. When one considers the present physiological experiments together with those of Denny-Brown and Russell,1 there appears to
be no doubt that functional alterations of brain concussion are the same in the rhesus monkey and the cat.

Our experiments suggest that the major feature of concussion of the brain is a transient paralysis of certain interneuron systems. The excitatory phenomena which we have observed in concussion in cats, monkeys and guinea pigs lightly anesthetized with chloralosane have been isolated, occasional and variable. In the monkey, possible evidences of stimulation were elevation of the upper eyelids, dilatation of the pupils, and struggle. In the cat they were dilatation of the pupils, withdrawal of the nictitating membrane, tonic contractions of the orbicularis oculi muscle, tonic contractions of the tongue musculature, and reduced thresholds of cranial motor nuclei and fiber bundles. In the guinea pig, tonic or clonic spasm of limb or trunk musculature was apt to occur at any time in the minutes following the blow. It is to be emphasized that all these manifestations were of isolated and occasional nature. The startle reflex which often could be observed upon impact in monkeys and cats was very slight and qualitatively was the same as, though in magnitude much less than, the startle response which could be elicited prior to concussion by clapping the hands or striking the table in the proximity of the animals.

The correlation between our physiologic results and our histologic observations is evident. Histologic alterations were encountered in certain upstream interneuron systems, including the motor cortex, but were most extensive and severe in the brain stem.

It should be emphasized that in experiments with monkeys, we were dealing with simple concussions, i.e., transient paralytic states setting in immediately upon application of an adequate force to the brain. In human clinical experience, concussion is often combined with traumatic interstitial hemorrhage, contusion or laceration of the brain. The latter three types of injuries, should not be given the unmodified designation, concussion. We would caution further that the several post-traumatic conditions should not be referred to loosely as concussion. Indiscriminate use of the term concussion and its equivalents has produced much confusion in the realm of traumatic brain injuries and their sequelae. We hope the present study will help form a basis for limiting its use.

SUMMARY

Concussions of the brain were induced in rhesus monkeys by striking the head with a pendulum apparatus, by dropping a weight on the piston of an hydraulic apparatus connecting with the interior of the cranium by means of a metal cannula, or by striking with a hammer a Wood's metal lifecast applied to the head. In acute physiologic experiments, it was demonstrated that differential functional alterations took place in the monkey as they did in the cat. Function of the motor cortex of the cerebrum and of other supranuclear regions was more adversely affected in concussion than was function of cranial motor nuclei. Corneal reflexes could be abolished
without significantly changing the threshold to stimulation of the motor neurons involved.

Histologic alterations were observed in the brains of monkeys that had been struck concussive blows six or eight days previously. These consisted of differential chromatolytic changes in certain interneuron systems of the brain stem and of other cytologic changes in the pyramidal cells of the motor cortex. Primary motor neurons of the cranial nerve nuclei were not affected. Immediate cytologic changes similar to those described previously in guinea pigs were observed in certain large neurons of the monkey’s brain. The structural changes appeared to be ascribable to uncomplicated concussion of the brain.

REFERENCES