transmits afferent pulses from the carotid sinus resulting in cardiovascular changes.

CHARLES HERBERT: Anatomical studies have shown that the nerve fibers making up the innervation of the carotid sinus are derived mainly from the cervical sympathetic and the glossopharyngeal nerve, and that loops of fibers exist communicating with the vagus and very rarely with the hypoglossal nerves. Knowledge of the function of the fibers from each of these sources has been gained indirectly or only guessed at, for heretofore no discreet distruction of all the fibers of one origin has been carried out and the result studied. The sympathetic fibers have been considered efferent, those of the 9th nerve afferent, while those of the vagus have been guessed to be afferent.

By sectioning the right 9th nerve intracranially in our patient we cut off from the brain those fibers innervating the carotid sinus derived from the glossopharyngeal nerve while maintaining intact those fibers from any other origin. Since by this one procedure the sensitivity of the right carotid sinus was abolished while that of the left carotid sinus remained, we might be justified in concluding that afferent fibers from sources other than the 9th nerve, if they exist at all, must be of little or no importance, at least as far as carotid sinus sensitivity, as we test it, is concerned.

The cardiac and vasomotor pressor response obtained by Dr. Ray by procanizing the region of a carotid sinus after section of the homolateral 9th nerve intracranially for reasons other than the treatment of and in patients not suffering from carotid sinus sensitivity, might have been due to the procaine acting somewhere systematically.

In our patient procainization of his right carotid sinus with 20 cc. of 2% procaine in addition to abolishing the carotid sinus sensitivity on that side caused a transient elevation of cardiac rate from 56 to 92 per minute and of blood pressure from 178/110 to 238/128. This pressor response is not unusual and is cited only for comparison with the elevation of pulse rate from 60 to 90 per minute and blood pressure from 180/105 to 210/120 obtained on another occasion by injecting the same dose of procaine into the deltoid muscle. I do not know whether Dr. Ray controlled his experiments in a similar way.

BRAIN CHANGES ASSOCIATED WITH ELECTRICALLY INDUCED SEIZURES

A STUDY IN THE MACACUS RHESUS

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Reports concerning the occurrence of pathological changes in the nervous system associated with electrically induced convulsions have been conflicting and often misleading. Experimental animals have been of many species (cats, rabbits, dogs, etc.). There has been little uniformity in the administration of the seizures, either as to frequency or current "dosage" and the procedures bear little or no relation to the

usual clinical course of therapy in human cases. In addition, there has been little use of control animal material in the pathological states reported. No studies have as yet been reported for the monkey.

The present study presents the observations on a series of 12 macacus rhesus monkeys subjected to electrically induced seizures under conditions resembling as closely as possible the administration of the treatment to human beings. Seizures were administered three times per week with voltages varying from 70-135 with current times of .10 or .15 seconds. It was possible to administer series of either minor seizures or major ones. The largest number of seizures administered was 30 convulsions with applied voltage of 135 and current passage time of .15 seconds. Electroencephalograms were recorded at frequent intervals during the course of seizures on the days between seizures.

When the desired number of seizures had been administered, the animals were sacrificed, usually 24 hours after the last seizure. Air embolism was used which resulted in rapid death. The brains and cords were removed immediately together with the other organs and placed in proper fixitives. Histological stains including methods for staining nerve cells, myelin sheaths, axis cylinders, glia, general topography (H&E) connective tissue and blood vessels were used.

Neuropathological findings were surprisingly meager even in animals subjected to a series of seizures well beyond that usually utilized in treatment clinically. An example is a monkey which received 30 generalized convulsions at a frequency of three per week at an applied potential difference of 135 volts and a time of current passage of .15 seconds. This is well within the upper range of both frequency and current time passage in human treatments, and the number of seizures is greater than usually used clinically. The results of neuropathological study with all the methods utilized were limited to nerve cell changes. There were no hemorrhages, petechial or gross. The blood vessels were normal. There were no pathological changes in the myelin sheath or axis cylinders. The microglia, oligodendroglia and astrocytes were normal throughout. The nerve cell changes were spotty in distribution and not localized to any particular portion of the brain. In the areas involved some of the nerve cells appeared shrunken with pyknosis of the nucleus, paling of the cytoplasm and disappearance of the Nissl substance. Some of the cells were only shadow cells. There was no pericellular glial reaction and the changes bore no relation to the blood vessels. Changes of this type occurred in small areas and the nerve cells immediately surrounding these areas were usually entirely normal. Such changes could be found in most of the animals treated with electric shock. The incidence of such "pathological" changes bore no direct quantitive relation to any of the characteristics of the series of seizures administered, i.e., frequency, number of seizures, voltage or current time passage, type of resulting seizure. In-

deed the significant result in this regard was that similar changes were found in the brains of untreated animals which were kept in the laboratory for similar periods of time and sacrificed purely for control purposes. The changes could therefore not be related to the electrically induced seizure and their significance in the general behavior of the animal seems relatively insignificant. It is felt by the authors that utilization of improper control material in animal experiments of this type has often resulted in erroneous reports as to significant pathological changes.

Despite the absence, however, of any definite relation between the seizures and the histological changes it was possible to demonstrate changes electroencephalographically which seemed of perhaps greater significance. The electroencephalographic changes associated with electrically induced seizures in monkeys parallel almost exactly those seen in human patients treated with electrically induced seizures. The changes in the human graphs were previously reported by the authors. There are several minor differences in the changes as seen in monkeys as compared with those in human beings. In the monkey it is somewhat more difficult to produce the severe type of change seen in patients with perhaps ten or a dozen generalized seizures. Then again, the pathological waves in the monkey tend to disappear more rapidly following cessation of seizures than in the usual human case.

It is felt by the authors that, in the macacus rhesus monkeys subjected to electrically induced seizures administered at frequency, voltages, and current times definitely within the range as utilized in human treatment, there is no evidence, on the basis of our work, to indicate a relation between electrically induced seizures and histopathological changes. Physiological evidence of dysfunction, however, as manifested in the electroencephalogram is as clear and definite as it is in the human patient and it is felt that the changes in the brain associated with electrically induced seizures as used clinically, are more probably of a physiological or perhaps chemical type than structural; at least as they could be detected by the use of the usual neuropathological technics.

On the possibility that concordance of some other abnormality in the organism (blood pressure, chemical or vitamin changes, etc., etc.) and electrically induced seizures might be correlated with a greater amount of pathological change, experiments are being initiated in monkeys to study this point.

DISCUSSION

MATTHEW T. MOORE: Dr. Barrera very modestly stated that he was going to add confusion to a topic which already was pretty well muddied up. I think, however, that he has helped to clarify the matter.

This morning I stated that there are probably a number of factors which tend to produce the histopathologic changes which have been reported as occurring in the brains of animals with experimentally produced convulsions induced by the

electric current. The changes to which I refer are subarachnoid hemorrhages and intra-cerebral petechial hemorrhages. I believe that these hemorrhages are due to a vulnerable vasculature resulting from nutritional deprivation plus the added disruptive factor of the passage of an electric current. As has so well been shown by Dr. Alexander this morning the passage of an electric current within the limits necessary to produce a convulsion, does not alter the angioarchitecture of the brain to the extent of producing hemorrhage. Furthermore, he showed that when the intensity of the current has been increased greatly in excess to that given in comparable human treatments, that these hemorrhages occur only in the "track" or path between the electrodes and are not diffusely distributed throughout the brain. I feel that the diffuse hemorrhages which have been reported are, first, probably due to factors frequently overlooked by laboratory workers, namely, that the brains of the animals, upon which they are experimenting, are not free of histopathologic alterations, and second, that they are due to the combined effects of a nutritional deficiency predisposing to vascular defects in the small cerebral vessels and the superimposed effect of the electric current.

Neumann, Cohn and Katzenelbogen have shown in a control group of untreated laboratory animals histopathologic changes in the brain such as cerebral congestion, stasis of blood vessels, pyknosis of the ganglion cells and even petechial hemorrhages. In evaluating the histopathologic findings in experimental animals it is essential to consider the factors of nutritional deprivation, "laboratory encephalitis," and perhaps other conditions before reaching hard and fast conclusions.

Lewis J. Pollock: Does the absence of demonstrable pathological lesions in the brain indicate that no damage has been done to the brain? This question occurs to me because of the very well known observation that when animals are experimentally exposed to the nearby detonation of high explosives and show unmistakable evidence of defective function of the nervous system, little or no pathology can be found in the central nervous system of such animals. The same thing is true in animals that are subjected to blows designed to produce traumatic concussion only. It seems to me that it is necessary to determine that we have sought for damage at the proper time, and that we have looked for the proper kind of damage. For example, Mahoney has shown in his experiments on traumatic concussion that fat emboli do occur, but also that they disappear after three hours following the concussion. It may be that if animals subjected to other forms of trauma to the head were examined sufficiently early, we likewise might find some evidence of injury.

In cases of accidental injury by electrical shock, Panse in particular has reported that one of the characteristic results is the occurrence of late vascular effects, many weeks or even months after the exposure to an electrical current. It may perhaps be quite likely that we will not find any destruction of the blood vessels soon after having subjected the animal to a number of seizures, but that these effects may occur much later.

An amusing situation arose here in Chicago in connection with the use of electric shock in our local stockyards. The kindness of the hearts of the people of Chicago could not contemplate with equanimity the killing of a hog without in some way first anesthetizing the animal. It occurred to the meat packers that perhaps they could anesthetize the animal by an electric current, with the production of a loss of consciousness and convulsions. But the rub was that when this was done, the hog had so many petechial hemorrhages in the lungs that the United States meat inspectors would not pass the carcasses because of the resemblance to hog cholera. What happens in the lung of man?

Abraham M. Rabiner: If, as is said, these animals are presumably normal although they show abnormal findings in the brain, how do you account for those patients who after electric shock treatment show such tremendous memory defects?

And how do you account for the fact that some of these patients, who first had a manic depressive psychosis, later develop epilepsy?

S. EUGENE BARRERA: I thank Dr. Moore for emphasizing the importance of comparative pathology. It is probably just as important as comparative physiology.

Dr. Pollock raised some very interesting questions which I do not pretend, and I do not think any of the other authors would pretend to be able to answer. Far be it from us to assume that, because these particular methods do not manifest changes, therefore, no pathological changes of any type have occurred. I will go even further than that and raise what seems to me to be a more difficult question to answer. Even if we did find changes present, which we definitely believe to be pathological, what is their significance as far as the status of the patient or the status of the monkey is concerned? We merely have two coordinates here in our two sets of observations and they are manifestly insufficient to solve our question. If we subject an animal or a patient to electric shock and then find certain neurohistological or pathological conditions in the brain, and also find that the patient shows some peculiarity in behavior, are we justified in assuming that the changes in the brain and behavior are casually related? I don't think any of us would even seriously consider that as a compelling conclusion at all. We would have to have some independent set of observations outside of that particular system in order to relate these two changes.

It is interesting that at least a month after we have terminated a long series of convulsions, we have not found a monkey as yet which has developed any vascular pathological change. I believe that Alexander's work showed that the changes which occurred with the passage of the current, or shortly thereafter subsided rather rapidly, at least as detected by the method which he used at the time. I do not know, of course, whether some vascular change could occur at a later date. If so we would then have the difficulty of establishing the casual relation between the late change and the treatment.

Dr. Rabiner gives me some food for thought, because as yet on the basis of a wide acquaintance with clinical results of this treatment, I have not come across any cases of patients with normal pre-treatment electroencephalograms who develop epilepsy following treatment. In our series of well over 300 cases now at the Psychiatric Institute, we have had one case which developed a spontaneous seizure six months after cessation of treatment. When we went back over our pre-treatment electroencephalograms, we found what appeared to be "a convulsive pattern" in that electroencephalogram. For that reason, we seriously recommend a routine electroencephalogram before any electric shock treatment is carried out. We must recall also that not so rare occurrence of spontaneous seizures reported due to barbiturate withdrawal.

I don't know how to account for the memory defect. I know that it occurs. I know it occurs in some patients much more definitely than in others. Interestingly enough, it seems to be most manifest in our experience in those cases which have a very large psychoneurotic element in the picture. In fact, even after two or perhaps three convulsions, these patients may appear to have a tremendous memory defect, and be greatly concerned over it; but I do not know the basis for this. I do not like to get entangled too much in what has been called "fueliginous tenebrosity" on this particular matter.

of convulsions of perhaps thirty minutes. So that I do not think the amount of current delivered over a long period, or the total time of the convulsions can be the crucial factor.

It seems to me that to say that the electrical shock or that the electrical current has nothing to do with the changes in the brain, if one assumes that there are changes in the brain, is simply begging the question. Let us assume that they are not responsible and that the current is not responsible for the brain changes. The current has been produced and whatever has taken place has been indirectly the result of the current and probably would not have been there if electrical shock had not been used. So that looked at it in a little more oblique sort of way, the electrical current is in some sense responsible for the brain changes, at least, which we found.

I think that there must be some other responsible factor. There may be a difference in species, or there may even be a different susceptibility of human beings to the electrical shock. There may be some X factor which, as Dr. Moore has pointed out, is present in such cases which develop changes in the brain. I do not think that we are in a position to say definitely what happens at the present time, but I think it is a good plan to speculate about it. It may be that the patients with some degree of inanition, or patients who seemingly are in good health but who have some obscure ailment are more susceptible to brain changes than are others. I do not see from the evidence which we have at hand that we can say that the electrical current is not responsible in any sense nor can we say that the changes which have been produced have not been produced by physiological methods.

HARRY C. SOLOMON: It is undoubtedly very important to have records of human beings who have died after electric shock, thus only can we get any real material from which to draw conclusions of what happens in the human being. However, I think we can heed carefully what Dr. Barrera has told us, that it is very difficult to draw conclusions and make too close connections.

May I refer to several points about Dr. Ebaugh's cases? One case that died of coronary disease is one of those accidents that are bound to occur. He may have died at the same day or a week later without the shock; but he did go through a convulsive period which was a drag. We all, I think, have known patients who had marked coronary disease and have been given electric shock therapy without having any bad results therefrom.

The second case, as I gather it, died of an anoxia and it would seem fair to assume that some of the cellular changes were the result of the anoxia. So perhaps had he not died of an anoxia, such axis-cylinder changes would not have taken place. What also is interesting was the diffuse location of the pathological findings which would seem to suggest at any rate that they were not due to the current, although they may have been due to the convulsions and to the changes that take place in the body with anoxia, with convulsion, and so on.

I would like again to emphasize that it is very difficult to draw the conclusion that these findings were the result either of any particular factor, electric shock, convulsion, anoxia or anything else; but with the accumulation of more such cases, we will have a very much better basis upon which to reach a conclusion. I think we must all constantly give homage to the great god coincidence, particularly when we only have a couple of cases to our credit.

I would like to add one more case of death following electric shock which occurred in one of our Massachusetts institutions, of which I am able to tell you something. This was a young man in the early twenties who had previously had a course of ten metrazol convulsions, with some improvement of his symptoms, a relapse, ten electric shock convulsions with again some improvement, followed by a relapse and return to the hospital, and then eight or nine more electric shocks.

Fifteen hours subsequent to the last shock, he died of pulmonary edema. Microscopic studies have not yet been made. Grossly there were no brain changes to be seen, certainly no gross or meningeal hemorrhages. He had an early but definite glomerular nephritis and the assumption (again being an assumption) is drawn that the combination of the glomerular nephritis plus the weight of the convulsive therapy upon his economy was sufficient to break him down and lead to pulmonary edema and death.

ABRAHAM MYERSON: I am going to stress what Dr. Solomon said about the great god coincidence. People have died of coronary thrombosis outside of the waiting room of the cardiologist just after they have been examined by competent cardiologists and have had electrocardiograms taken.

The number of deaths from coronary thrombosis which occur suddenly without any exciting cause that can be found makes one say that the burden of proof is not on the man who gives the electric shock or the general use of electric shock treatment, but upon the individual who states that a coronary thrombosis following treatment had anything to do with the electric shock treatment.

The second thing I want to express is perhaps more radical. I believe there have to be organic changes or organic disturbance in the physiology of the brain for the cure to take place. I think the disturbance in memory is probably an integral part of the recovery process. I think it may be true that these people have for the time being at any rate more intelligence than they can handle and that the reduction of intelligence is an important factor in the curative process. I say this without cynicism. The fact is that some of the very best cures that one gets are in those individuals whom one reduces almost to amentia. It is impossible to conceive of that amentia without an organic base; there must be at least temporarily organic changes in the brain, and the cure is related to these organic alterations. Possibly there is occasioned, in some instances, more or less irreversible pathology, but in the vast majority of individuals this is not true. In these cases and for the time being something happens to the brain which interferes with its function sufficiently so that mood becomes altered in the proper direction. I think that we need not be afraid of this particular phase of the situation. We need not be worried lest we be producing permanent organic changes in the brain. Every surgical operation in an interference with normal physiology and is a multilation and likewise this particular type of drastic therapy is associated, I believe, with reversible and transitory organic changes in most instances, possibly with irreversible organic changes in a very few.

NATHANIEL W. WINKELMAN: Dr. Myerson has touched upon something which is very interesting, but I think there is something else we must consider. I would like to ask those who have been interested in the pathology of the nervous system over a period of many years whether or not they couldn't duplicate what Dr. Ebaugh has shown in a 57- or 58-year-old man, irrespective of electric shock. I would like also to ask them also whether or not they have found hemorrhages in the brain in status epilepticus. I have seen a good many cases of patients who have died in status; no hemorrhages were found. I have seen gross hemorrhages only where patients in a convulsion have fallen down the stairs or hit their heads against radiators. Where there has been this direct relation between trauma and the convulsion, there is a different story. I think the case that Dr. Alpers quoted as proof of his hemorrhage theory is reported in full in the last number of the Neuropathologic Journal. I think that is right. I think Dr. Alpers reported that death occurred two months after the last treatment and that the hemorrhage in that case was *fresh* blood. I certainly would not by any stretch of imagination attribute that lesion to a therapeutic convulsive course completed two months before death.

The changes that Dr. Barrera reported are significant and I agree that there are and must be changes of a reversible nature.