What of natural migrations, particularly those which cross long stretches of ocean, or those in which young birds seem to migrate along the route characteristic of the species without adults to guide them? Clearly, one should not speculate too widely on the basis of one experiment with a single species, but it would perhaps be pertinent to re-examine the evidence concerning the directness of natural migratory flights. Could it be that transocean migrants, for example, do *not* fly straight in the absence of landmarks—or such cues as wind direction —but rely, under difficult conditions at least, on some type of exploratory searching for their goal? Since observations of the usual type tell us little or nothing about the actual flight paths of individual birds, we cannot safely infer from them that a migrant flies along an essentially straight course, although this has generally been assumed to be the case, just as it has been assumed for the return flights of homing birds.

To be sure, the important experiments of Rowan (*4*), Rüppell (*5*), and Schüz (*6*) have shown that inexperienced young birds may migrate in approximately the correct direction even without adults to guide them. These flights were over land with many landmarks available, the problem being to explain how the birds selected the appropriate cues to guide their first fall migration southward. But it seems unnecessary to conclude, as many have done (*2*, *3*, *7*), that birds must possess an unknown sensory mechanism capable of informing them of their latitude and longitude, or the equivalent, so that they can travel to their nest or winter range, as the case may be, without reliance on such mundane cues as landmarks, the position of the sun, or wind direction. Neither the observed flight paths of homing gannets and herring gulls nor the indirect evidence that other homing birds rely on landmarks and exploration (*1*) are consistent with these theories. Merely as an example of an alternate explanation for the results obtained by Rowan, Rüppell, and Schüz, it should be noted that the birds were released north of 50° latitude, where even in summer the sun is always perceptibly south of the zenith. Rowan's releases were made in Alberta during November, when the sun never rises more than 20° above the horizon. Thus, a tendency to fly toward the sun could perhaps account for the southward movement of these inexperienced birds.

In so far as our conclusions are relevant for other species under other conditions, they suggest that birds do not possess a special "sense of direction" or any sensitivity to the earth's magnetic field. The behavior of the gannets reinforced our impression that birds navigate by means of environmental cues which lie within the scope of the known receptors. When landmarks (rivers, coastlines, mountain ranges, etc.), prevailing winds, or the direction of the sun are not available as guiding influences, or when birds are released in unknown territory where the environmental cues have no meaning, they may well reach their goal by a process of exploration. There is need, however, for more observations from the air of the actual flight paths of other birds, both during homing flights and during migration, and one can perhaps look forward to a solution of this classic problem of biology as investigators make greater use of aircraft and other fruits of modern technical ingenuity.

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A Mechanism of Concussion: A Theory[1]

James W. Ward, L. H. Montgomery, and Sam L. Clark

Department of Anatomy, Vanderbilt University Medical School, Nashville, Tennessee

The similarity of the forms of pressure waves generated by two entirely different methods, both of which cause cerebral concussion, has led us to formulate a theory of the physical mechanism of concussion. One method, a standard one, involves the striking of the head of an animal by a mass of known weight and velocity. In the second method, a percussion wave was set up in water in which the head of an animal was partly submerged. This procedure was employed to prevent skull distortion as much as possible. The apparatus used in these experiments was similar to that described by Clark and Ward (*2*) but produced pressure waves many times as strong. When the top of the head of a small animal (guinea pig) received a pressure wave of sufficient strength, concussion resulted as judged by certain generally accepted criteria for concussion in animals ("start reaction" with the blow, loss of corneal reflexes, temporary inhibition of respiration, etc.). The bony air sinuses of the animal's head were kept just above the surface of the water at the moment of impact in order to mitigate the effects of the pressure wave on the brain via the sinuses (*25*).

The general problem of the mechanism or mechanisms of concussion raises two prime questions. First, how do effective forces bring about the changes in function of the nervous elements in the brain to give symptoms of concussion? Second, what types of forces are capable of eliciting these changes?

With respect to the first question, several mechanisms have been postulated. These have been discussed by Denny-Brown and Russell (*4*), who discarded many of them because they are based on inadequate data. Two underlying processes associated with concussion have considerable experimental evidence supporting them: excitation and inhibition (paralysis) of the neurons of the

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Vanderbilt University.

brain. Emphasis has been placed on one or the other at various times, e.g., on paralysis by Denny-Brown and Russell (*4*) and on excitation followed by "physiological extinction" by Walker, Kollros, and Case (*24*). Both of these processes probably occur in concussion, as the experiments of Krems, Schopfle, and Erlanger (*16*) suggest. They conclude that "concussion would be accounted for . . . by stretch blocks of neurons plus excitation at the distorted foci, when there was evidence of excitation."

Considerable disagreement exists as to the type of force capable of causing concussion. Walker, Kollros, and Case (*24*) assume that oscillations in pressure are responsible for stimulation of neurons, but it seems exceedingly likely that the method of recording employed (Hamilton manometer) may give rise to misleading results due to the low natural frequency inherent in this system (*10*). Denny-Brown and Russell (*4*) have implicated acceleration as a basis of concussion leading to "direct traumatic paralysis of nervous function." Holbourne (*13*), however, has indicated that in a tissue with a high bulk modulus (relative incompressibility) and a low modulus of rigidity like the brain, the only type of stress likely to produce damage is a shearing one. Shearing forces develop with angular acceleration, and even in the absence of skull distortion from a blow, they would be capable of causing damage. Denny-Brown and Russell (*4*) found that a skull of a cat could be indented as much as 5 mm by a blow without causing fracture. Even less indentation of a skull of such size might lead to considerable reduction in volume with displacement of the nervous tissue toward the natural openings of the skull. This, in turn, could give rise to strong shearing displacements within the brain.

In our experiments small wire strain gages mounted on a small brass or copper cylinder (*18*) were used for recording pressures. These gages were inserted into the brain of a decapitated cat through the foramen magnum or, for the second type of experiment, were placed in the water, where they were subjected to rapid and intense pressure waves generated in it (*2*). Figs. 1 and 2 show the results obtained in these two conditions.

Considerable positive pressure lasting a few thousandths of a second was developed (200–700 lbs/in² or more) either in the percussion wave in water or in the head of the cat when it was struck by the falling weight. Negative pressure (tension), lasting a thousandth of a second or more, also occurred (20–75 lbs/in²). This degree of tension appears to be possible because of the rapid development of the negative pressure and because of the viscosity and inertia of the water.

Positive pressures in the lower range (several hundred atmospheres), even though considerably prolonged, exert little effect other than a stimulation of physiological processes in living tissues. Cattell (*1*), summarizing the physiological effects of pressure, concludes that "any influence of hydrostatic pressure must be secondary to a decrease in volume." Since the coefficient of compressibility of water, the chief constituent of the brain, is 44.2×10^{-6} at 20° C in the range of 100–200 atm (*26*), it is probable that little significant change in volume is likely to occur in the ranges under consideration. Marsland and Brown (*17*) have observed only a cessation of

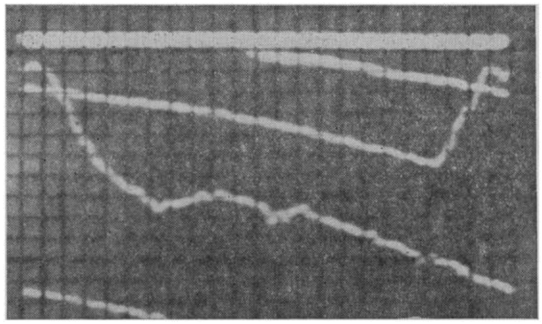

FIG. 1. Recording of a pressure wave generated within the brain of a decapitated cat when the skull was struck by a weight (937 gm) which had fallen 5′. The weight was stopped by a mechanical stop within 5 mm after impact with the skull. The surface of impact on the weight was a ball bearing ¾″ in diameter. Horizontal sweep speed of C.R.O.: 1 small square represents 1/2,760 sec. A continuous sweep was used and triggered to drop at approximately a constant rate just before the pressure wave reached a small strain gage inserted into the brain of the cat through the foramen magnum. Pressure calibration: 1 small vertical square equals 25 lbs/in².

The positive pressure wave lasted approximately 1/400 sec and reached 125 lbs/in²; the negative pressure wave, about 1/700 sec and reached a value of between 15 and 20 lbs/in² below atmospheric pressure.

activity of *Amoeba proteus* and *A. dubia* when they are exposed suddenly to 250 atm of pressure. Regnard (*21*) found that fresh-water fish whose swim bladders had previously been emptied of air showed no effect when 100 atm of pressure was applied to them. Gaertner (*7*) applied 25 atm of pressure to mice and noticed no ill effects with either slow or rapid application. Grundfest and Cattell (*9*) studied nerve conduction in the sciatic nerve of the frog under the effects of hydrostatic pressure. Increase in excitability characteristics resulted from mod-

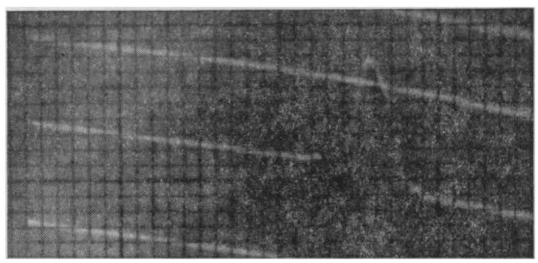

FIG. 2. Recording of a pressure wave generated in water capable of producing the symptoms of concussion in a guinea pig. A cylindrical strain gage was used in the water. Calibration: 1 small vertical square equals 100 lbs/in². Sweep speed: 1 small horizontal square equals 1/8,000 sec. The positive pressure wave reached a peak of about 700 lbs/in² and lasted 1/2,000 sec while the negative pressure wave had a value of 75–100 lbs/in² and lasted 1/1,000 sec.

erate pressure (5,000–8,000 lbs/in²), but this was lost at higher levels (around 15,000 lbs/in²).

On the other hand, negative pressures appear to be the ready source of damage to living tissue. Johnson (*14*) found that supersonic sound waves caused the destruction of red blood cells suspended in the radiated fluid. He was able to prevent their destruction by applying a positive hydrostatic pressure of 65 lbs/in² to the entire system during radiation. This has generally been interpreted as indicating that the destruction of the cells was caused by cavitation during radiation when the system was at atmospheric pressure (*22*). It is thought that the rapid shifting of fluid which results from cavitation causes a tearing of the cells. Distortion by compression and stretching is an intermediate effect of cavitation in such a system. Harvey and Loomis (*12*), who took stroboscopic pictures of *Arbacia* eggs (diameter, 75 μ) during the course of supersonic radiation, found that specific eggs disappeared within the space of time from one picture to the next (1/1,200 sec). While in all probability this does not represent a minimum time for the formation of cavities in such a system, it indicates that the duration of negative pressure in the brain following a blow on the head or a percussion wave transmitted to the brain through water (1/700 sec and 1/1,000 sec, respectively) is sufficient to cause the formation of cavities.

Some of the available information on the mechanism of formation of bubbles within liquids in the presence of negative pressures should be considered. Harvey (*11*) has discussed the relation between "gas nuclei" and bubble formation in an analysis of decompression illness. Gas nuclei appear to be of considerable importance for the formation of bubbles in liquids where conditions are constant or changing slowly (*5, 15*). Rapidly changing conditions, however, lead readily to bubble formation (*15*) and, as Dean (*3*) has shown, the easiest method for the formation of bubbles in a solution is to introduce vortices in the fluid.

Little information is present concerning the formation of bubbles in fluids of the body under negative pressure. Harvey (*11*) has studied the effects of negative pressure just below the partial pressure of blood and with careful technic has shown that bubbles will not be formed in blood under such pressure. He found, however, that controlled muscular exercise will cause the formation of bubbles in the blood of an animal when it is placed in a pressure chamber at 110 mm Hg. He likens this observation to those resulting from the tapping of a test tube of water free of gas nuclei and immediately lowered to the same pressure. No studies are available which give direct evidence on bubble formation in body fluids at much lower pressures (below absolute zero).

Since it has not been actually possible to demonstrate transient cavities within the brain, we performed the following model experiment, not unlike one described by Harvey (*11*). Specially prepared 5% gelatin in test tubes was subjected to the rapid pressure wave in water of sufficient strength to cause concussion in guinea pigs when only the tops of their heads were subjected to the pressure wave. These tubes of gelatin were prepared by evacuating them for 30 min at an absolute pressure of 55 mm Hg during the period of cooling from 140° F to room temperature. This was done to remove trapped air on particles in the solution, and incidentally the gelatin solution was considerably degassed by the process. The right-hand tube in Fig. 3 shows that no bubbles were formed in the solidified gelatin when this tube was evacuated to 55 mm Hg. Immediately, however, bubbles appeared in another tube of gelatin (left) which had been prepared like the first, except that it had been subjected to the percussion wave in water just before being placed under the same negative pressure. When the pressure was applied only briefly to the last tube, all but the largest bubbles disappeared when the pressure was returned to atmospheric level. These experiments with the

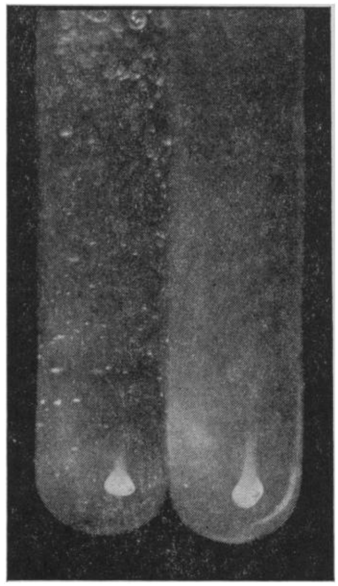

FIG. 3. See text for description of the experiment. Both tubes were at room temperature, and the picture was taken when both were under 55 mm Hg absolute pressure.

degassed gelatin involving the rapid changes in pressure states, both positive and negative (as shown by Figs. 1 and 2), suggest strongly that transient bubbles may be formed within the fluid of the brain when such pressure waves are introduced. It is quite likely that bubble formation is even more easily accomplished in the latter situation in the face of the strong negative pressures developed because of the saturation of the fluid phase of the brain by oxygen and, particularly, carbon dioxide (*11*).

The small vibrations appearing during the negative phase of the pressure waves, as recorded in Figs. 1 and 2, probably represent indications of the development of bubbles in the brain of the decapitated cat and in the water, respectively. Further evidence for this is obtained from the following experiments: Test tubes of vacuum-pump oil (instead of water) in which a strain gage had been placed were subjected to percussion waves in water (Fig. 4).[2] It is evident that the negative pressure wave following the positive pressure is steeper, and, proportional to the positive pressures recorded in Figs. 1 and 2, it is much greater. The explanation seems to lie in the difference in vapor pressures of the various media (and the dissolved gases?). When test tubes of water were held under a vacuum (at 27 mm Hg, absolute pressure) for as much as ½ hr, during which they were tapped repeatedly, the mercury column in the manometer dropped as much as 4 mm with each tap toward the end of this time and was accompanied by violent but brief "boiling" of the water. Upon similar treatment of the vacuum-pump oil, vigorous "boiling" also occurred, but no movement of the mercury column could be detected. (In these experiments the vacuum obtained without water in the system or with the oil present was 17 mm Hg. The pressure on the water after ½ hr evacuation and tapping was 27 mm Hg.) While it is not likely that great negative pressures (tension) would be developed in the brain following a blow to the skull, as indicated by these experiments, the production of bubbles would be relatively easy because of the partial pressure of the fluid in the brain and its dissolved gases.

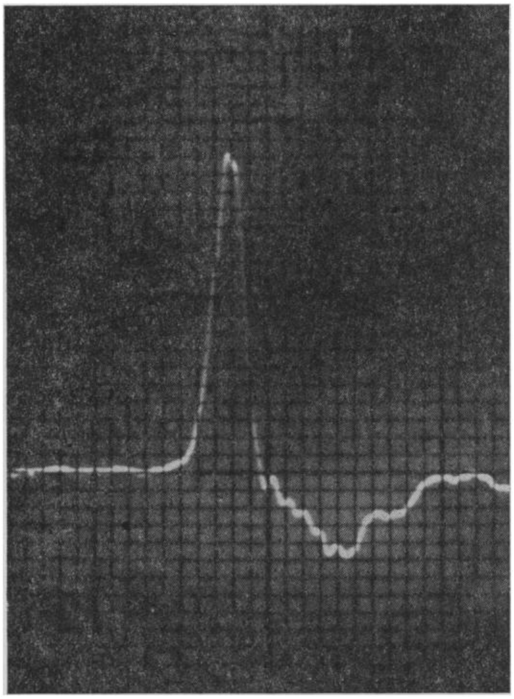

FIG. 4. The recording of a pressure wave in Cenco Hyvac oil. Calibration: 1 small scale vertical division equals 50 lbs/in². Sweep speed: 1 small scale division equals 1/10,000 sec. A positive pressure of 900 lbs was reached and lasted for 2/5,000 sec. A negative pressure of 225 lbs/in² followed and lasted about 1/1,000 sec.

The theory we would advance, then, is that damage to nervous tissue can result from a blow on the head or from the passage through it of an intense, rapid pressure wave delivered to it through water, chiefly as a result of the process of cavitation, *i.e.* "formation and vehement collapse of cavities" (*23*). This process, occurring during and following the negative phase of the pressure wave passing through the head, could lead to the production of transient local shearing forces which would affect nerve cells, fibers, synapses, and, if strong enough, even small blood vessels. These shearing forces could cause stimulation and/or blocking of nervous activity of varying degrees in various parts of the brain by distortion, depending on a number of variable factors (strength of force applied, direction of its application, rapidity of application, etc.).

These cavities may be exceedingly small, and probably are, because of the short duration of the negative pressure and of the inertia of the tissue fluids. They probably do not need to be large to cause damage, for the cavities which lead to the destruction of *Arbacia* eggs during supersonic radiation (*12*) were not visible with a magnification of approximately 25 diameters. The effect would thus be quite local. Since the number of cavities formed under such conditions may be related to the number of gas molecules in a given volume of tissue (*19*), a certain scattering of the cavities might be expected. This situation may explain the scattered distribution of chromatolytic cells which Groat, Windle, and Magoun (*8*) found in the brains of experimental animals suffering "uncomplicated concussion."

In the recording of the pressure waves in water we have seen that low-amplitude positive pressures are followed by little or no negative pressure. The theory, therefore, explains the absence of concussion when crushing forces are slowly applied to the skull (*6*). Explosive blasts, particularly in air, in the absence of the head being struck by a flying object, etc., appear to be a poor cause of uncomplicated concussion. This may be explained by the fact that, as a shock wave proceeds from its place of origin, its front becomes steeper during the time it has great energy, while the falling face of the positive pressure becomes flattened (*20*), and the factor for the production of great negative pressure is, therefore, reduced. In water, where negative pressure (tension) greater than absolute zero can occur, an explosion is likely to cause uncomplicated concussion only if the falling face of the positive pressure wave is rapid enough to be followed by considerable negative pressure, no matter how strong or how rapid the original pressure rise.

[2] This figure was reproduced in a previous article (*18*).

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IN THE LABORATORY

Methods for Labeling Thyroxine With Radioactive Iodine[1]

Earl Frieden, Mortimer B. Lipsett, and Richard J. Winzler

Department of Biochemistry and Nutrition, University of Southern California School of Medicine

In order to study the metabolism of thyroxine it became necessary to consider the methods for labeling thyroxine with I^{131} and the positions of the radioactive iodine atoms. We wish to report on two methods that we have used to prepare radiothyroxine of high activity.

Radiothyroxine has been prepared by Horeau and Suë (*3*) from 3,5-diiodothyronine using the method of Harington and Barger (*2*), in which the iodinating agent is iodine in ammoniacal solution. It has been assumed that the compound so prepared is 3′,5′-di-I^{131},3,5,di-I^{127} thyronine. This supposition is of some importance in experiments dealing with the fate of injected thyroxine, since differences undoubtedly exist in the reactivities of the iodines of the two rings. Thus, deiodination *in vivo* may proceed preferentially at one or the other rings, and a knowledge of the position of the iodine atoms is pertinent.

The total synthesis of thyroxine by the classical method of Harington and Barger (*2*) does not offer a practical route for the preparation of the tetra-I^{131}-labeled thyroxine. This is due to the relatively short half-lives of the available iodine isotopes and an over-all yield of less than 5% in the 10-step procedure.

Labeled thyroxine has also been isolated after the injection of I^{131} into animals with functioning thyroid glands as well as after incubation of thyroid slices with I^{131} (Morton, Chaikoff, *et al.*, *5*). However, these biosynthetic methods are not practical for the preparation of radiothyroxine of high specific activity in the amounts needed for biological work. It is likely that thyroxine so prepared contains I^{131} distributed among the four positions.

A simple and convenient technique for preparing radiothyroxine was suggested by the work of Miller, *et al.* (*4*), who studied the exchange reactions of diiodotyrosine with iodine and iodide ion. They found that at pH 5 and 50° C iodine exchanged almost completely with the iodine of diiodotyrosine in 90 min.

We have similarly prepared radioactive thyroxine by an exchange reaction. In a typical experiment 5 mg of *dl*-thyroxine was introduced into 25 ml of a 9:1 butanol-water mixture at pH 5 containing 0.10 mg of I^{127} and 10 μc of I^{131} as the iodides. After being refluxed for 12 hrs, the mixture was cooled and any undissolved thyroxine removed by filtration and thoroughly washed. The remaining butanol solution was washed to remove inorganic iodide and the butanol removed *in vacuo*. The thyroxine fractions were then recrystallized from boiling 0.1 N sodium carbonate solution. In several runs, up to 30% of the radioactive iodine could be recovered in the recrystallized thyroxine. This, of course, indicates that under these conditions complete exchange was not achieved. However, with this exchange reaction, using an initial radioactivity of 10 mc of I^{131} in the solution, it should be possible to prepare 5-mg quantities of radiothyroxine with an activity of greater than 10^6 disintegrations/μg/min and thus study the metabolism of thyroxine when given at *physiological levels*.

Since we have no evidence as to whether or not all the iodine atoms in thyroxine are involved in this exchange, data obtained with this radiothyroxine may be subject to the limitation discussed above for the preparation of radiothyroxine from 3,5-diiodothyronine. The question of which iodine atoms are involved in this exchange will be difficult to solve. Previous methods employed by Har-

[1] Aided by a grant from Eli Lilly and Company.