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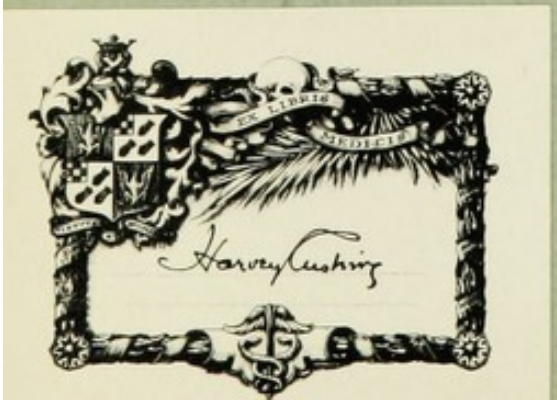

Phylogenetic Association in Relation to Certain Medical Problems

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Cleveland, Ohio

Ether Day Address

1910

The Barta Press, Boston

PHYLOGENETIC ASSOCIATION IN RELATION TO CERTAIN MEDICAL PROBLEMS.*

The discovery of the anesthetic properties of ether and its practical application to surgery must always stand as one of the great achievements of medicine. It is eminently fitting that the anniversary of that notable day, when the possibilities of ether were first made known to the world, should be celebrated within these walls, and whatever the topic of your Ether Day orator, he must fittingly first pause to pay tribute to that great event and to the master surgeons of the Massachusetts General Hospital. On this occasion, on behalf of the dumb animals as well as on behalf of suffering humanity, I express a deep sense of gratitude for the blessings of anesthesia. Two years ago an historical appreciation of the discovery of ether was here presented by Professor Welch, and last year an address on medical research was given by President Eliot. I, therefore, will not attempt a general address, but will present an experimental and clinical research.

Time will permit the presentation of only the summaries of the large amount of data. The great assistance rendered by my associates, Dr. D. H. Dolley, Dr. H. G. Sloan, Dr. J. B. Austin and Dr. M. L. Menten†, I acknowledge with gratitude.

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*Address delivered at the Massachusetts General Hospital on the sixty-fourth anniversary of Ether Day, Oct. 15, 1910.

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The scope of the title of this paper may be explained by a concrete example.

When a barefoot boy steps on a sharp stone there is an immediate discharge of nervous energy in his effort at escape from the wounding stone. This is not a voluntary act. It is not due to his own personal experience (i.e., his ontogeny), but is due to the experience of his progenitors during the vast periods of time required for the evolution of the species to which he belongs, i.e., his phylogeny. The wounding stone made an impression upon the nerve receptors in the foot similar to the innumerable injuries which gave origin to this nerve mechanism itself during the boy's vast phylogenetic or ancestral experience. The stone supplied the phylogenetic association, and the appropriate discharge of nervous energy automatically followed. If the sole of the foot is repeatedly bruised or crushed by the stone, shock may be produced. If the stone be only lightly applied, then there is also a discharge of nervous energy from the sensation of tickling. The body has had implanted within it in a similar manner other mechanisms of ancestral or phylogenetic origin whose purpose is the discharge of nervous energy for the good of the individual. In this paper I shall discuss the origin and mode of action of some of these mechanisms including certain phases of anesthesia.

The word anesthesia — meaning *without feeling* — describes accurately the effect of ether in anesthetic dosage. Although no pain is felt in operations under inhalation anesthesia, the *nerve impulses set up* by a surgical operation still reach the brain. We know that not every portion of the brain is fully anesthetized, since surgical anesthesia does not kill. The

question then is, What effect has trauma under surgical anesthesia upon the part of the brain *that remains awake?* If, in surgical anesthesia, the traumatic impulses cause an excitation of those wide-awake cells, are the remainder of the cells of the brain, despite anesthesia, influenced in any way? If influenced, they are prevented by the anesthesia from expressing the same in conscious perception or in muscular action. Whether the *anesthetized* cells are influenced or not must be determined by noting the physiologic function after anesthesia has worn off, and in animals by an examination of the brain cells as well. It has long been known that the vasomotor, the cardiac and the respiratory centers discharge energy in response to traumatic stimuli applied to various sensitive regions of the body during surgical anesthesia. If the trauma is sufficient, exhaustion of the entire brain is observed after the effect of the anesthetic is worn off; that is to say, despite the complete paralysis of voluntary motion and the loss of consciousness due to ether, the traumatic impulses that are known to reach the *awake* centers in the medulla also reach and influence every other part of the brain. As to whether or not the consequent functional depression and the morphologic alterations seen in the brain cells may be due to the low blood pressure which follows excessive trauma is answered by the following experiments, viz: the circulation of animals was first rendered *static* by over-transfusion, and was controlled by a continuous blood-pressure record on a drum, the factor of anemia was thereby wholly excluded during the application of the trauma and during the removal of a specimen of brain tissue for histologic study. In every such instance morphologic changes in the cells

of all parts of the brain were found, but it required more trauma to produce *equal* morphologic changes in animals protected against low blood pressure than in animals whose blood pressure gradually declined in the course of the experiments.

In the cortex and in the cerebellum, the changes in the brain cells were in every instance more marked than in the medulla. There is also strong *negative* evidence that traumatic impulses are not excluded by ether anesthesia from the part of the brain that is apparently asleep. This evidence is as follows :

If the factor of fear be excluded, and if in addition the traumatic impulses are prevented from reaching the brain by cocaine blocking, then, despite the intensity or the duration of the trauma within the zone so blocked, there follows no exhaustion after the effect of the anesthetic disappears, and no morphologic changes are noted in the brain cells. A still further negative evidence that inhalation anesthesia offers little or no protection to the brain cells from trauma is derived from the following experiment : A dog whose spinal cord had been divided at the level of the first dorsal segment, and then kept in good condition for two months, showed a recovery of the spinal reflexes, such as the scratch reflex, etc. This animal is known as a "spinal" dog. Now, in this animal the abdomen and hind extremities have no direct nerve connection with the brain. In such a dog a continuous severe trauma of the abdominal viscera and of the hind extremities lasting four hours was accompanied by but slight change in either the circulation or in the respiration, and no microscopical alteration of the brain cells. Judging from a large number of experiments on *normal* dogs under ether, such an amount

of trauma would have caused not only a complete physiologic exhaustion of the brain, but also morphologic alterations of all of the brain cells and physical destruction of many. We must, therefore, conclude that, although ether anesthesia produces unconsciousness, it *apparently protects none of the brain cells* against exhaustion from the trauma of surgical operations; ether is, so to speak, but a veneer. Under nitrous oxide anesthesia there is approximately only one-fourth the exhaustion on equal trauma as under ether; either nitrous oxide protects or ether predisposes to exhaustion under trauma. With this as a point of departure we will inquire into the cause of this exhaustion of the brain cells.

On the Cause of the Exhaustion of the Brain Cells from Trauma of Various Parts of the Body Under Inhalation Anesthesia.

Numerous experiments on animals upon the effect of ether anesthesia *per se*, *i.e.*, ether anesthesia without trauma, showed that although certain changes were seen there was neither the characteristic physiologic exhaustion after the anesthesia had worn off nor were there seen the characteristic changes in the brain cells. Turning to trauma, in a study of the behavior of individuals as a whole under deep and under light anesthesia, we at once found the cue to the discharge of energy, — the consequent physiologic exhaustion and the morphologic changes in the brain cells.

If, in the course of abdominal operations, rough manipulation of the parietal peritoneum is made, there is frequently observed a marked increase in the respiratory rate and an increase in the expiratory force,

even to the extent of an audible expiratory groan. Under light ether anesthesia severe manipulation of the peritoneum often causes such vigorous contractions of the abdominal muscles that the operator may be greatly hindered in his work.

Among the unconscious responses to trauma under ether anesthesia are purposeless moving, withdrawing of the injured part, and if the anesthesia is sufficiently light and the trauma sufficiently strong, there may be an effort directed toward escape from the injury. In injury under ether anesthesia every grade of response may be seen, from the slightest change in the respiration or in the blood pressure to a vigorous defensive struggle. As to the purpose of these subconscious movements in response to injury, there can be no doubt, — *they are efforts at escape from the injury.*

Can anyone picture the actual result of a formidable abdominal operation extending over a period of half an hour or more in an unanesthetized human patient if extensive adhesions are broken up, or if a large tumor is dislodged from its bed? In such a case would not the nervous system discharge its energy to the utmost in efforts to escape from the injury, and would the patient not suffer complete exhaustion? If the traumata, under inhalation anesthesia, be sufficiently strong and repeated in sufficient numbers, the brain cells will finally be deprived of their dischargeable nervous energy and become exhausted just as exhaustion follows a strenuous and too prolonged muscular exertion, for example, such as is seen in endurance tests. Whether the nerve energy of the brain is discharged by injury under anesthesia, or whether by ordinary muscular exertion, identical morphologic changes are seen in the nerve cells. In

shock from injury, in exhaustion from overwork (Hodge and Dolley) and in exhaustion from pure fear, the general functional weakness is similar, — in each a certain length of time is required to effect recovery, and in each there are morphologic changes in the brain cells. It is quite clear that in each of these cases the altered function and form of the brain cells are due to an *excessive discharge of nervous energy*. This brings us to the next question, viz: what determines the discharge of energy from trauma with or without inhalation anesthesia?

On the Cause of the Discharge of Nervous Energy from Trauma in Animals Under Inhalation Anesthesia as Well as in the Normal State with Special Reference to Medical Problems.

I looked into this problem from many view-points and there seemed to be no solution until it occurred to me to seek the explanation in certain of the postulates which make up the doctrine of evolution. I realize fully the difficulty and the danger in attempting to reach the generalization which I shall make later and in the hypothesis I shall propose. There is, of course, no direct final proof of the truth of even the doctrine of evolution. It is idle to consider any experimental research into the cause of phenomena that have by natural selection required millions of years to develop. Nature has made the experiments on a world-wide scale; the data are before us for interpretation. Darwin could do no more than collect all available facts and then frame an hypothesis that best harmonized the facts. Sherrington, that masterly physiologist, in his volume entitled "The Integrative

Action of the Nervous System," shows clearly how the central nervous system was built up in the process of evolution. Sherrington has made free use of Darwin's doctrine in explaining physiologic functions, just as anatomists have extensively utilized it in the explanation of the genesis of anatomical forms. I will assume, therefore, that the discharge of nervous energy is accomplished by the application of the law of inheritance and association, and that this hypothesis will explain many clinical phenomena. I shall present such evidence in favor of this hypothesis as time and my limitations will admit, after which I shall point out certain clinical facts that may be explained on this hypothesis.

According to the doctrine of evolution, every function owes its origin to natural selection in the struggle for existence. In the lower and simpler animal life, indeed, in our human progenitors as well, existence depended principally upon the success with which three great purposes were achieved, viz: (1) self-defense against or escape from enemies; (2) the acquisition of food; and (3) procreation; and these were virtually the only purposes for which nervous energy was discharged. In its last analysis in a biologic sense this statement holds for man of to-day. Disregarding for the present the expenditure of energy for procuring food and for procreation, we will consider the discharge of energy in self-preservation. The mechanisms for self-defense which we now possess were developed in the course of vast periods of time from the lowest forms through all the intermediary stages to our present estate. One would expect, therefore, that we are now in possession of mechanisms which still may discharge energy on adequate

stimulation but are not suited to our present needs. We shall point out such examples. As Sherrington has stated, there is interposed between ourselves and the environment in which we are immersed, our skin, in which are implanted many receptors for receiving specific stimuli which are transmitted to the brain. When these stimuli reach the brain, there is a specific response principally in the form of muscular action. Now, each receptor can only be adequately stimulated by the particular factor or factors in the environment which created the necessity for the receptor in question. Thus there have arisen receptors for touch, for temperature, for pain, etc. The receptors for pain have been designated noci-ceptors (nocuous or harmful influences) by Sherrington.

On the basis of natural selection, only the regions of the body that have been during long periods of time exposed to injury could have developed noci-ceptors. On this ground the finger, because it is exposed, should have many noci-ceptors, while the brain, though the most important organ of the body, because it has been during a vast period of time protected by a skull, should have no noci-ceptors. Realizing that this point is a crucial one, Dr. Sloan and I made a series of careful experiments. The cerebral hemispheres of dogs were exposed by removal of the skull and dura under ether anesthesia and under local anesthesia. Then various portions of the hemispheres were slowly but completely destroyed by rubbing with a piece of gauze. In some instances the hemisphere was destroyed by burning. In no instance was there more than a slight response of the centers governing circulation and respiration, and there was no morphologic change noted in a histologic study of the brain cells of the uninjured hemis-

phere. The experiment was as completely negative as the experiments on the "spinal" dog. Clinically I have confirmed the experimental findings in the course of explorations for brain tumor with a probe in conscious patients. Such explorations elicited neither pain nor evidence of altered physiologic functions. The brain, therefore, contains no mechanism, — no noci-ceptors, — the direct stimulation of which could cause a discharge of nervous energy in a self-defensive action. That is to say, direct injury of the brain can cause no purposeful nerve muscular action, while direct injury of the finger does cause purposive nerve muscular action. In like manner, the deeper portions of the spinal region have been sheltered from trauma, and they too show but little power of causing a discharge of nervous energy on receiving trauma. The various tissues and organs of the body are differently endowed with injury receptors, or the noci-ceptors of Sherrington. The abdomen and chest when traumatized stand first in their facility for causing the discharge of nervous energy, i.e., *they stand first in shock production*. Then follow the extremities, the neck and the back. It is an interesting fact that *this* physical type or *that* physical type of trauma elicits different responses as to the discharge of energy. Because it is such a commonplace, one scarcely realizes the importance of the fact that clean-cut wounds with a razor-like knife cause the least reaction, while a tearing, crushing trauma causes the greatest response. It is a suggestive fact that the technic of the carnivora in fighting each other and in killing their prey is probably the most efficient shock-producing trauma known. *In the course of evolution this may well have been the predominating type of trauma to which our progenitors were subjected.*

The discharge of energy caused by an adequate mechanical stimulation of the noci-ceptors is best explained in accordance with the law of phylogeny and association. That is, injuries awaken such reflex actions as have by natural selection been developed for the purpose of self-protection. Adequate stimulation of the noci-ceptors for pain is not the only means of causing a discharge of nervous energy. Nervous energy may also be discharged by adequate stimulation of the various ticklish regions of the body. The entire skin surface of the body contains delicate ticklish receptors. These receptors are closely related to the noci-ceptors for pain, and their adequate stimulation by an insect-like touch causes a discharge of energy — a nerve muscular reaction — resembling that of brushing off insects. This reflex is similar to the scratch reflex elicited in the dog. This discharge of energy is almost wholly independent of the will and is a self-protective action in the same sense as is the response to pain stimuli. The ear in man and in animals is acutely ticklish, — the adequate stimulus being any foreign body, — especially a buzzing insect-like contact. The discharge of nervous energy in horses and in cattle on adequate stimulation of the ticklish receptors of the ear is so extraordinary that in the course of evolution it must have been of great importance to the safety of the animal. A similar ticklish zone guards the nasal chambers. The discharge of energy here takes such form as effectively to dislodge the foreign body. The larynx is exquisitely ticklish, and in response to adequate stimulus, energy is discharged in the production of a vigorous cough. The mouth and pharynx have active receptors which cause the rejection of nocuous substances. The con-

junctival reflex, though not classed as ticklish, is a most efficient self-protective reflex. I assume that there is no doubt as to the meaning of the adequate stimuli and the nerve-muscular response of the various ticklish receptors of the surface of the skin, of the ear, the nose, and the eye, and the larynx. These mechanisms were developed by natural selection as protective measures against the intrusion of insects and foreign bodies into regions of great importance. The discharge of energy in these instances is in accordance with the law of inheritance and association. The other ticklish points which are capable of discharging vast amounts of energy are the lateral chest wall, the abdomen, the loins, the neck and the soles of the feet. The type of adequate stimuli of the soles of the feet, the distribution of the ticklish points upon them, and the associated response leave no doubt that these ticklish points were long ago established as a means of protection from injury. Under present conditions they are of little value to man.

The adequate stimulus for the ticklish points of the ribs, the loins, the abdomen and the neck is deep isolated pressure, probably the most adequate being that of a tooth-shaped body. The response to tickling in these regions is actively and obviously self-defensive. The horse discharges energy in the form of a kick ; the dog wriggles and makes a counter-bite ; the man makes efforts at defense and escape.

There is strong evidence that the deep ticklish points of the body were acquired through vast periods of fighting, with teeth and claws. Even puppies at play bite each other in their ticklish points and thus give a recapitulation of their ancestral battles and of the real battles to come. The mere fact that animals fight effectively

in the dark and always according to the habit of their species supports the belief that the fighting of animals is not an intellectual but a reflex process. There is no book of rules governing the conduct of a fight between animals. The sequences of events follow each other with such kaleidoscopic rapidity that the process is but a series of automatic stimulations and physiologic reactions. Whatever the significance, it is certain that man did not come either accidentally or without purpose into possession of the deep ticklish regions of his chest and abdomen. Should any one doubt the vast power that adequate stimulation of these regions possess in causing the discharge of energy, let him be bound hand and foot and vigorously tickled for an hour. What would happen? He would be as completely exhausted as though he had experienced a major surgical operation or as if he had run a Marathon race.

A close analogy to the reflex process in the fighting of animals is shown in the rôle played by the sexual receptors in conjugation. Adequate stimulation of these two distinct groups of receptors, the noci and the sexual, cause specific behavior, — the one toward embrace, the other toward repulsion. Again, one of the most peremptory causes of the discharge of energy is that due to an attempt forcibly to obstruct the mouth and the nose, threatening asphyxia. Neither friend nor foe is trusted, and a desperate struggle for air ensues. It will be readily granted that the efforts to prevent suffocation were established for the purpose of self-preservation, but the discharge of nerve-muscular energy to this particular end is no more specific and no more shows adaptive qualities than do the preceding examples. Even the proposal

to bind one down hand and foot excites resentment, a feeling of self-preservation. No patient views with equanimity the application of shackles preparatory to anesthesia for an operation.

We have now considered some of the causes of the discharge of nervous energy due to various types of harmful physical contact, and have suggested analogous though antithetical sexual receptors. The response to the adequate stimuli of each of the several receptors is a discharge of nerve muscular energy of a specific type: One type for the ear, one for the larynx, one for the pharynx, another for the nose, another for the eye, another for the deep ticklish points of the chest and the abdomen, quite another for the delicate tickling of the skin, and still another in response to sexual and to painful stimuli.

According to Sherrington, a given receptor has a low threshold for only one, its own — hence a specific stimulus and a high threshold for all others; that is, the doors that guard the nerve paths to the brain are opened only on receiving the proper password. According to Sherrington's law, the individual as a whole responds to but one stimulus at a time; that is, only one stimulus occupies the nerve paths which perform acts, i.e., the final common path. As soon as a stronger stimulus reaches the brain it dispossesses whatever other stimulus is then occupying the final common path, — the path of action. The various receptors have a definite order of precedence over each other (Sherrington). For example, the impulse from the delicate ticklish points of the skin whose adequate stimulus is an insect-like contact could not successfully compete for the final common path, with the stimulus of a noci-ceptor. The stimulus of a fly on

the nose would be at once superseded by the crushing of a finger. In quick succession do the various receptors (Sherrington) occupy the final common path, but each stimulus is for the time always the sole possessor, hence the nervous system is integrated (connected up) to act as a whole. Each individual at every moment of its life has a limited amount of dischargeable nervous energy. This energy is at the disposal of any stimulus that obtains possession of the final common path, i.e., the *performance of acts*. Each discharge of energy is subtracted from the sum total, and whether the subtractions are made by the excitation of noci-ceptors by trauma, by tickling, by fighting, by fear, by flight or by the excitation of sexual receptors, singly or in combination, the sum total of expenditure of energy, if large enough, produces exhaustion. Apparently there is no distinction between that state of exhaustion which is due to the discharge of nervous energy in response to trauma and that due to other causes. The manner of the discharge of energy is specific for each type of stimulation. On this conception traumatic shock takes its place as a natural phenomenon and is divested of its mask of mystery.

The Discharge of Energy Through Stimulation of the Distance Receptors, or Through Representation of Injury (Psychic).

We will now turn from the discussion of the discharge of nervous energy by mechanical stimuli to the discharge of energy through mental perception. *Phylogenetic* association may arise through the distance receptors as well as through physical contact, viz: through sight, hearing, smell, or by a repre-

sentation of physical experiences. The effect upon the organism of the representation of injury or of the perception of danger through the distance receptors is designated *fear*. Fear is as widely distributed in nature as is its cause, that is, fear is as widely distributed as injury. Animals under the stimulus of fear, according to W. T. Hornaday, not only may exhibit preternatural strength, but also show strategy of the highest order, a strategy not seen under a lesser stimulus. In some animals fear is so intense that it defeats escape; this is especially true in the case of birds in the presence of snakes. The power of flight has endowed the bird with an easy means of escape from snakes, especially when the encounter is in the tops of trees. Here the snake must move cautiously else he will lose his equilibrium. His method of attack is by stealth. When the snake has stalked its prey, the bird is often so overcome by fear that it cannot fly and so becomes an easy victim. The phenomena of fear are described by Darwin as follows:

"Fear is often preceded by astonishment and is so near akin to it that both lead to the senses of sight and hearing being instantly aroused. In both cases the eyes and mouth are widely opened and the eyebrows raised. The frightened man at first stands like a statue, motionless and breathless, or crouches down as if instinctively to escape observation. The heart beats quickly and violently, so that it palpitates or knocks against the ribs. That the skin is much affected under the sense of fear, we see in the marvelous and inexplicable manner in which perspiration immediately exudes from it. This exudation is all the more remarkable as the surface is then cold, and hence the term, 'a cold sweat'; whereas the sudorific glands

are properly excited into action when the surface is heated. The hairs also on the skin stand erect, and the superficial muscles shiver. In connection with the disturbed action of the heart, the breathing is hurried. The salivary glands act imperfectly; the mouth becomes dry and is often opened and shut. I have also noticed that under slight fear there is a strong tendency to yawn. One of the best marked symptoms is the trembling of all the muscles of the body, and this is often first seen in the lips. From this cause, and from the dryness of the mouth, the voice becomes husky and indistinct, or altogether may fail. As fear increases into agony of terror, we behold, as under all violent emotions, diversified results. The heart beats wildly, or may fail to act, and faintness ensue; there is a death-like pallor; the breathing is labored; the wings of the nostrils are dilated; there is a gasping and convulsive motion of the lips, a tremor on the hollowed cheek, a gulping and catching of the throat; the uncovered and protruding eyeballs are fixed on the object of terror, or they may roll restlessly from side to side. The pupils are said to be enormously dilated. All the muscles of the body become rigid, or may be thrown into convulsive movements. The hands are alternately clenched and opened, often with a twitching movement. The arms may be protruded, as if they were to avert some dreadful danger, or may be thrown wildly over the head. In other cases there is a sudden and uncontrollable tendency to headlong flight; and so strong is this, that the boldest soldier may be seized with a sudden panic. As fear arises to an extreme pitch, the dreadful scream of terror is heard. Great beads of sweat stand on the skin. All the muscles of the body are relaxed. Utter prostration

soon follows, and the mental powers fail. The intestines are affected. The sphincter muscles cease to act and no longer retain the contents of the body. Men during numberless generations have endeavored to escape from their enemies or danger by headlong flight, or by violently struggling with them; and such great exertions will have caused the heart to beat violently, the breathing to be hurried, and the chest to heave, and the nostrils to be dilated. As these exertions have often been prolonged to the last extremity, the final result will have been utter prostration, pallor, perspiration, trembling of all the muscles, or their complete relaxation. And now, whenever the emotion of fear is strongly felt, though it may not be from any exertion, the same results tend to reappear, through the force of inheritance and association." (*Darwin.*)

In an experimental research, we found evidence that the physiologic phenomena of *fear* have a physical basis. This evidence is morphologic alterations in the brain cells, similar to certain stages of surgical shock and in fatigue from muscular exertion. For the present we will assume that fear is a *representation* of trauma. Because fear was created by trauma, fear causes a discharge of the energy of the nervous system on the law of phylogenetic association. The almost universal fear of snakes, of blood and of death and dead bodies, may have such a phylogenetic origin. It was previously stated that under the stimulus of fear animals show preternatural strength. An analysis of the phenomena of fear shows that, so far as can be determined, all of the functions of the body requiring the expenditure of energy and which are of no direct assistance in the effort toward self-preser-

vation are suspended. In voluntary expenditure of muscular energy, such as in the chase, the suspension of other functions is by no means so complete. Fear, hence trauma, may, therefore, drain to the last dreg the dischargeable nervous energy; therefore, the greatest possible exhaustion may be produced by fear and trauma. This is a distinction between fear and desire.

There is a factor, however, that influences the discharge of energy which I must discuss briefly. I refer to summation.

Summation.

In the discharge of energy, summation plays an important rôle. Summation is attained by the repetition of stimuli at such a rate that each succeeding stimulus is applied before the nerve cells have returned to the resting stage from the preceding stimulus. If drops of water fall upon the skin from a sufficient height to cause the slightest unpleasant sensation, and at such a rate that before the effect of the stimulus of one drop has passed another drop falls in precisely the same spot, there will be felt a gradually increasing painful sensation until it becomes unbearable. This is summation. When a patient requires for a long time frequent painful wound dressings, there is a gradual increase in the acuteness of the pain receptors. This is summation. In a larger sense the behavior of the entire individual gives considerable evidence of summation, e.g., in the training of athletes the rhythmic discharge of muscular energy at such intervals that the resting stage is not reached before a new exercise is given results in a gradual ascent in efficiency until the maximum is reached. This is summation, and

summation plays a large rôle in the development of both normal and pathologic phenomena.

We have now pointed out the manner in which at least a part of nervous energy of man may be discharged. The integrative action of the nervous system and the discharge of nervous energy by phylogenetic association may be illustrated by the analogy of an electric automobile. The electric automobile is composed of three principal parts: the motor and the wheels (the muscular system and the skeleton); the cells of the battery containing stored electricity (brain cells, nervous energy); and the controller which is connected with the cells by wiring (the receptors and the nerve fibers); and an accelerator button for increasing the electrical discharge (thyroid gland?). The machine is so constructed that it acts as a whole for the accomplishment of a single purpose. When the controller is adjusted for going ahead (adequate stimulus of a receptor), then the conducting paths (the final common path) for the accomplishment of that purpose are all open to the flow of the current from the battery, and the vehicle is integrated to go ahead. It spends its energy to that end and is closed to all other impulses. When the controller is set for reverse, the machine is by this adequate stimulus integrated to back, and the battery is closed to all other impulses. Whether integrated for going forward or backward, if the battery be discharged at a proper rate until exhausted, the cells, though possessing no more power (fatigue), have sustained no further impairment of their elements than that of normal wear and tear. Furthermore, they may be restored to normal activity by recharging (rest). If the vehicle be placed against a stone wall, and the controller be placed at top speed

ahead (trauma and fear), and if the accelerator is on as well (thyroid secretion?), though the machine will not move, the battery will not only soon be exhausted, but the battery elements themselves will be seriously damaged (exhaustion, — surgical shock).

We have now presented some evidence that nervous energy is discharged by the adequate stimulation of one or more of the various receptors that have been developed in the course of evolution. In response to an adequate stimulus, the nervous system is integrated for the specific purpose of the stimulated receptor, and but one stimulus at a time has possession of the final common path,— the nerve mechanisms for action. The most numerous receptors are those for harmful contact. These are the noci-ceptors. The effect of the adequate stimulus of a noci-ceptor is like that of pressing an electric button that sets in motion great machinery.

With this conception, the human body is likened to a musical instrument,— an organ, the keyboard of which is composed of the various receptors upon which environment plays the many tunes of life; and written within ourselves in symbolic language is the history of our evolution. The skin may be the "Rosetta Stone" which furnishes the key.

Anoci-Association.

We are now prepared on the law of phylogenetic association to make a practical application of the principles of the discharge of nervous energy. In the case of a surgical operation, if fear be excluded and if the nerve paths between the field of operation and the brain be blocked with cocaine, there will be no discharge of energy due to the operation; hence, there

can be no shock, no exhaustion. Under these conditions of operation the nervous system is protected against noci-association whether by noci-perception or by an adequate stimulation of noci-ceptors. The state of the patient in whom all noci-associations are excluded can be described only by coining a new word. That word is "*anoci-association.*"

The difference between anesthesia and anoci-association is that although *inhalation anesthesia* confers the beneficent loss of consciousness and freedom from pain, it does not prevent the nerve impulses from reaching and influencing the brain, and hence does not prevent surgical shock nor the train of later nervous impairments so well described by Mumford. *Anoci-association* excludes fear, pain, shock and post-operative neuroses. *Anoci-association* is accomplished by a combination of special management of patients (applied psychology), morphine, inhalation anesthesia and local anesthesia.

We have now presented in summary much of the mass of experimental and clinical evidence we have accumulated in support of our principal theme, viz: that the discharge of nervous energy is accomplished by the law of phylogenetic association. If this point seems to have been labored, it is because we expect to rear upon this foundation a clinical structure. How does this hypothesis apply to surgical operations?

Prevention of Shock by the Application of the Principle of Anoci-Association.

Upon this hypothesis a new principle in operative surgery is founded, viz: operation during the state of *anoci-association.* Assuming there is no unfavorable

effect of the anesthetic, and no hemorrhage, the nerve cells of the brain cannot be exhausted in the course of a surgical operation except by fear, or trauma, or by both. Fear may be excluded by narcotics and special consideration until the patient is rendered unconscious by inhalation anesthesia. Then in addition to inhalation anesthesia, blocking with cocaine the nerve paths between the brain and the field of operation will place the patient in the beneficent state of *anoci-association*, and at the completion of the operation the patient will be as free from shock as at the beginning. In so-called "fair risks" such precautions may not be necessary, but in cases handicapped by infections, by anemia, by previous shock and by Graves' disease, etc., anoci-association may become vitally important.

Graves' Disease.

Applying the principle of the discharge of nervous energy by phylogenetic association, and on the additional hypothesis that in the discharge of nervous energy the thyroid gland is, through the nervous system, stimulated, we can explain many phenomena of Graves' disease and possibly supply some of the factors to explain both the genesis and the cure of the disease.

In the wild state of animal life in which only the fittest survive in the struggle for existence, every point of advantage may have selection value. An animal engaged in battle or in a desperate effort at escape will be able to give a better account of itself if it has some means of accelerating the discharge of energy, some influence like that of oil upon the kindling fire. There is evidence, though perhaps not conclusive, that such an influence is exerted by the thyroid gland. This evidence is as follows: In myxe-

dema, a condition characterized by a lack of thyroid secretion, there is a dulness of reflexes, and of intellect, a lowered muscular power, and generally a sluggish discharge of energy. In Graves' disease there is an excessive production of thyroid secretion. In this disease the reflexes are greatly sharpened, energy is discharged with very greatly increased facility, and metabolism is at a maximum. The same holds true in the administration of thyroid extract in large doses in normal subjects. In the course of sexual activities there is an increased action of the thyroid as indicated by an increased size and vascularity of the thyroid. In fear and in injury in cases of Graves' disease the thyroid is probably stimulated to increased activity as indicated by the increased activity of the thyroid circulation, by an increase in the size of the gland, by presenting the histologic appearance of activity in the nucleus of the cells, and by an increase of the toxic symptoms. Finally, Asher has stated that electric stimulation of the nerve supply of the thyroid causes an increased secretion. The origin of many cases of Graves' disease is closely associated with some of the causes of the discharge of nervous energy, especially depressive influences, such as nervous shocks, worry and nervous strain, disappointment in love, business reverses, illness and death of relatives and friends. The association of activity of the thyroid with procreation is well known, hence the incidence of the double strain of overwork or of fear and the sexual evolution in maturing girls is obviously favorable to the development of Graves' disease. The presence of a colloid goiter is a suitable soil for the development of Graves' disease. I fully recognize the evidence that infection or auto-intoxication

may be contributing factors and must be assigned their rôle.

I have never known a case of Graves' disease to develop from success or from happiness alone, nor from hard physical labor, unattended by strain, nor from the results of energy voluntarily discharged. Some cases seem to have had their origin in over-dosage of thyroid extract in too vigorous an attempt to cure a colloid goiter. In Graves' disease one of the most striking characteristics is the patient's loss of control and an increased susceptibility to stimuli, especially to trauma and to fear and to the administration of thyroid extract. It has been shown that the various causes of the discharge of nervous energy produce alterations in the nervous system and probably in the thyroid gland. This is especially true of the fear stimulus. This is clearly demonstrated in the brains of rabbits subjected to fear alone. Of special interest is the effect of daily fright. In this case the brain cells show a distinct change, although the animal is subjected to no fear for twenty-four hours before it is killed. Now, a great distinction between man and the lower animals is the greater control man has acquired over his actions. This quality of control, having been phylogenetically most recently acquired, is the most vulnerable to various *nocuous* influences. The result of a constant noci-integration may be a wearing out of the control cells of the brain. In Graves' disease there has been demonstrated in a typical case a marked morphologic change in the brain cells. As previously stated, the origin of many cases of Graves' disease is associated in a broad sense with some noci-influence. If this influence causes stimulation of both the brain and the thyroid, its ex-

cessive action may cause impairment of the brain and hyperplasia of the thyroid as well. As self-control is impaired, fear obtains ascendency and, *pari passu*, would stimulate the thyroid still more actively. Finally, the fear of the disease itself becomes a noci-stimulus. As the thyroid secretion causes an increase in the facility for the discharge of nervous energy, there is established a pathologic reciprocal interaction between the brain and the thyroid. The effect of the constantly recurring stimulus of the noci-influence is heightened by summation. This reciprocal goading may continue until either the brain or the thyroid is destroyed. If the original noci-stimulus is withdrawn before the fear of the disease becomes too strong, and before too much injury to the brain and the thyroid has been inflicted, a spontaneous cure may result. Cure may be greatly facilitated by a complete rest cure. A cure implies the return of the brain cells to their normal state, with the re-establishment of the normal self-control, and the restoration of the thyroid to its normal state. Then the impulses of daily life will once more have possession of the final common path and the noci-influence be dispossessed. The discovery of the real cause of a given case of Graves' disease is frequently difficult because the exciting cause may be personal and is painful. Of extreme interest is the fact that the patient in the acute stage may be unable to refer to the real cause without exhibiting an exacerbation of the symptoms of the disease. I presume no case should be regarded as cured until reference can be made to the cause without an abnormal reaction. It has been established that in Graves' disease injury to any part of the body even under inhalation anesthesia causes an exacerbation of the disease.

Fear alone may cause an acute exacerbation. These acute exacerbations are frequently designated "hyperthyroidism" and are the special hazard of operation.

In operating on subjects of Graves' disease on the principle of anoci-association, there is scarcely a change in the pulse, in the respiration or in the nervous state at the close of the operation. Against the effect of the inflowing stimuli from the wound after the cocaine has worn off I know no remedy. It is necessary, therefore, in the serious cases not to venture too far. Since the adoption of this new method (anoci-association) my operative results have been so vastly improved that I now regard no case of Graves' disease as inoperable, at least to the extent of making a double ligation.

If we believe that a continuous stimulation of both the brain and the thyroid gland, on the law of phylogenetic association, accelerated by summation, plays a rôle in the establishment of the pathologic interaction seen in Graves' disease, then it is but the next step to assume that if the nerve connection between the brain and the thyroid is severed, or if the lobe is excised and the patient is reinforced by a sojourn in a sanatorium, or some environment free from former noci-association, the patient will, providing the brain cells, the heart or other essential organs have not suffered irreparable damage, be restored to normal health. There are still many missing links, and the foregoing is not offered as a final solution, although many of the phenomena from the view-point of the surgeon are explicable.

Sexual Neurasthenia.

The state of sexual neurasthenia is in many respects analogous to that of Graves' disease. In the

sexual reflexes summation leads to hyper-excitability to psychic and mechanical stimuli of a specific type analogous to the hyper-excitability in Graves' disease to trauma and fear; both are based on the law of the discharge of energy by phylogenetic association and summation. It would be interesting to observe the effect of interrupting the nerve impulses from the field of the sexual receptors by injections of alcohol or other agencies and thus exclude the associational stimuli until the nervous mechanism has again become restored to the normal.

Interpretation of Some of the Phenomena of Certain Diseases of the Abdomen on the Hypothesis of Phylogenetic Association.

On the law of phylogenetic association, it is probable that many of the phenomena of certain lesions in the abdominal cavity become explicable. The noci-ceptors in the abdomen, like noci-ceptors elsewhere, have been established by some kind of injury to which this region has been frequently exposed over vast periods of time. On this premise, we could at once predict that there are no noci-ceptors for heat within the abdomen because during countless years the intra-abdominal region has not come in contact with heat. That this inference is correct is shown by the fact that the application of a thermocautery to the intestines when completing a colostomy in a conscious patient is absolutely painless. One could also predict the fact that there are no touch receptors in the abdominal viscera, hence no sense of touch in the peritoneum. Just as the larynx, the ear, the nose, the sole of the foot and the skin have all developed the specific type of noci-ceptors which are adapted

for their specific protective purposes, and when adequately stimulated respond in a specific manner on the law of phylogenetic association, so the abdominal viscera have developed equally specific noci-ceptors as a protection against specific nocuous influences. The principal harmful influences to which the abdominal viscera may have been long exposed are deep tearing injuries by teeth and claws in the course of the innumerable struggles of our progenitors with each other and with their enemies; the perforation of the intestinal tract from ulcers, injuries, appendicitis, gallstones, etc., causing peritonitis; and over-distention of the hollow viscera from various forms of obstruction. Whatever may be the connection, it is a fact that the type of trauma from fighting corresponds nicely to that which in the experimental laboratory causes the most shock. Division of the intestines with a sharp knife causes no pain, but pulling on the mesentery elicits pain. Likewise, ligature of the stump of the appendix causes sharp cramp-like pains. Sharp division of the gall bladder causes no pain, but distention, which is the gall bladder's most common pathologic state, produces pain. Distention of the intestines causes great pain, but sharp cutting or burning causes none. In the abdominal viscera, like the superficial parts, noci-ceptors have been presumedly developed by specific harmful influences, and each noci-ceptor is open to stimulation only by the particular type that produced it.

As we have just stated, pain is associated with the excitation of noci-ceptors, and these may take precedence over and dispossess the routine functions, such as peristalsis, secretion and absorption, of their occupancy of their respective nervous mechanisms, just as

fear does. Hence, the loss of weight, the lassitude, the indigestion, the constipation and the many alterations in the function of the various glands and organs of the digestive system in chronic appendicitis, chronic gall-bladder disease, may be explained. This hypothesis readily explains the extraordinary improvement in the digestive functions and the general health following the removal of an appendix so slightly altered physically that only the clinical results in many cases could persuade one that this change could be an adequate cause for such far-reaching and important symptoms. It would equally explain certain gall-bladder phenomena — the indigestion, loss of weight, disturbed functions, etc. This hypothesis may supply the explanation of the disturbance from an active anal fissure, which is a potent noci-associator, and the consequent disproportionate relief after the trivial operation for its cure. Noci-association would well explain the great functional disturbances of the viscera immediately following abdominal operations.

Post-operative and traumatic neuroses are at once explained on the ground of noci-association, with the resulting strain upon the brain cells, causing in them physical lesions. If one were placed against a wall and were looking into the gun muzzles of a squad of soldiers and were told that he must not be afraid because in nine chances out of ten he would not be killed outright when the volley was fired, would it help him to be told that he must not be afraid? Such an experience would be written indelibly on his brain. Yet this is much the same position in which some surgical patients are placed. In railway wrecks we can readily understand the striking difference between the conscious passenger and the sleeping or drunken

one. In the latter persons the noci-ceptors and receptors were not aroused, hence their immunity. In the functional disturbances of the pelvic organs association and summation may play a large rôle. On this hypothesis many cases of neurasthenia may well be explained. In the behavior of the individual as a whole summation may well be a scientific expression for "nagging." Many other pathologic phenomena may be explained in a similar manner. Thus we can better understand the variation of a gastric analysis in a timid patient alarmed over his condition and afraid of the hospital. He is integrated by fear, and fear taking precedence over all other impulses, no organ functionates normally. On the same ground, one sees animals in captivity pine away under the dominance of fear. The exposure of a sensitive brain to the naked possibility of death from a surgical operation is equal to uncovering a photographic plate in the bright sunlight to inspect it before putting it in the camera. This principle explains, too, the physical influence of the physician or surgeon who, by his *personality*, inspires, like a Kocher, absolute confidence in his patient. The brain through its power of phylogenetic association controls many processes that have wholly escaped from the notice of the "practical man." It is on the law of association that a flower, a word, a touch, a cool breeze, or even the thought of a fishing rod or of a gun, are helpful. On the contrary, any fragment of associational evidence of despair or misfortune, whether it be the corrugated brow, the gloomy silence of despair, a doubtful word, is equally depressing, and so could one add indefinitely to the symbolism that governs our daily lives. Thus, we see that through the law of inheritance and noci-asso-

ciation, we are able to read into the behavior of various diseases a new meaning.

Observations on Patients Whose Associational Centers Are Dulled, and on Diseases and Injuries of Regions not Endowed with Noci-ceptors.

Reversing the order, let us glance at the patient who is unconscious and who, therefore, has lost much of the power of association. His mouth is usually dry, the digestive processes are at a low ebb, the aroma of food causes no secretion of saliva. Tickling the nose causes no sneezing; he catches no cold. The laryngeal reflex is lost and food may be quietly inhaled. The entire process of metabolism is low. The contrast between man with associational centers keen and man with these centers dulled or lost is the contrast between life and death. On the behavior of the individual without associational power much might be said.

On the laws of adaptation through natural selection, phylogeny and association, one should expect no pain in abscess of the brain, in abscess of the liver, in pylephlebitis, in infection of the hepatic vessels, in endocarditis. This law explains why there are no noci-ceptors for cancer, and active noci-ceptors for the acute infections, because against cancer nature has no helpful response to offer and in certain of the acute pyogenic infections the noci-ceptors give the beneficent physiologic rest.

Could we dispossess ourselves of the shackles of psychology, and forget its confusing nomenclature, and view the human brain, as Sherrington has said, "as the organ of, and for, the adaptation of nervous reaction," many clinical phenomena would appear in a clearer light.

Natural Selection and Chemical Noci-association in the Infections.

Heretofore we have considered the behavior of the individual as a whole in response to a certain type of noci-influences. We have been thinking in terms of physical escape from *gross* physical dangers, or grappling with *gross nerve-muscular* enemies of the same or of other species, as related to some problems in medicine. To explain these phenomena we have invoked the aid of the laws of natural selection and phylogenetic association. If our conclusions are correct, then it should follow that in the same laws we can find the explanation of immunity, which, of course, means a defensive response to our *microscopic* enemies. There should be no more difficulty in building up by natural selection an efficient army of phagocytes, or specific chemical reactions against *microscopic enemies*, than the building up of the various noci-ceptors for our muscular defense against our *gross enemies*. That immunity is a chemical reaction is no hindrance to the application of the law of natural selection nor of association. What essential difference is there between the chemical defense of the skunk against its *nerve-muscular* enemies and its chemical defense (immunity) against *its microscopic enemies?*

The administration of vaccines becomes the adequate stimuli by phylogenetic association of a chemical nature whereby immune bodies are produced.

While mentioning this subject I will only raise the question whether or not the specific character of the inaugural symptoms of some infectious diseases may not be due to phylogenetic association. These inaugural symptoms are measurably a recapitulation of

the leading phenomena of the disease in its completed clinical picture. Thus the furious immediate phenomena of pneumonia, of peritonitis, of erysipelas, of the exanthemata, show phenomena of exaggeration which are analogous to the phenomena of physical injury and of fear of physical violence. Just as the acute phenomena of fear or the adequate stimulus of noci-ceptors are a recapitulation of phylogenetic struggles, so may the inaugural symptoms of infections be a similar phylogenetic recapitulation of the course of the disease. A certain amount of negative evidence is supplied by the difference between the response of a dose of toxins as compared with a dose of a standard drug. No drug in therapeutic dosage except the iodine compounds causes a febrile response ; no drug causes a chill ; all specific toxins cause febrile responses, and many cause chills. If a species of animal had been poisoned by a drug over vast periods of time, and if natural selection had successfully established a self-defensive response, then the administration of that drug would cause the noci-association (chemical), and a specific reaction analogous to that following Coley's toxins might be expected. Bacterial noci-association probably operates through the same law as the physical contact of environment does. But natural selection is impartial. It must be supposed that it acts upon the microscopic invader just as well as upon the host. On this ground one would infer that the bacteria of acute infections must have met by natural selection each advance of the immunity of the host by the same law of natural selection. Hence, the fast and furious struggle between man and his microscopic enemies merely indicates to what extent natural selection has de-

veloped the *attack* and the *defense* respectively. This is analogous to the quick and decisive battles of the carnivora when fighting among themselves or when contending against their ancient enemies. But when phylogenetically strange animals meet each other, they do not understand how to conduct a fight. Natural selection has not had the opportunity of teaching them. The acute infections have the characteristics of being ancient enemies. On this hypothesis one might understand the high mortality of measles when introduced into a new country. The infecting agency of measles by natural selection has become a powerful enemy of the human race, but the particular race to whom this infection is newly introduced has not had the equal advantage of building up its defense by the same law — natural selection. The variation in the effect of auto- and iso-pollution of water may be explained in a similar manner. Immunity and food assimilation are, therefore, on equal footing. May not the phenomena of anaphylaxis be studied on associational lines? Then, too, there may be chemical noci-associations of enemies now extinct, which like the ticklish points may still be active on adequate stimulation. This brief reference to the possible relation of the phenomena of the acute infections to the laws of natural selection and specific chemical noci-association has been made as a suggestion. Since the doctrine of evolution is all or nothing, I have included many phenomena to see how reasonable or unreasonable such an explanation might be.

Recapitulation.

The following are the principal points presented: In operations under inhalation anesthesia the nerve im-

pulses from the trauma reach every part of the brain,—the cerebrum that is apparently anesthetized as well as the medulla that is known to remain awake, the proof being the *physiologic* exhaustion of and the *pathologic* change in the nerve cells. Under ether anesthesia the damage is at least four times greater than under nitrous oxide. Inhalation anesthesia is, therefore, but a veneer, a mask that "covers the deep suffering of the patient." The cause of the exhaustion of the brain is the discharge of nervous energy in a futile effort to energize the paralyzed muscles in an effort at escape from the injury just as if no anesthetic had been given. The exhaustion is, therefore, of the same nature as that from over-exertion.

But if the nerve paths connecting the field of operation and the brain be blocked, then there is no discharge of nervous energy from the trauma, and consequently no exhaustion however severe or prolonged the operation.

Fear is a factor in many injuries and operations. The phenomena of fear probably are exhibited only by animals whose natural defense is nerve-muscular. The skunk, the porcupine, the turtle, have little or no fear. Fear is born of the innumerable injuries in the course of evolution. Fear, like trauma, may cause physiologic exhaustion of and morphologic changes in the brain cells. The representation of injury, which is fear, being elicited by phylogenetic association, may be prevented by the exclusion of the noci-association or by the administration of drugs like morphine and scopolamine, which so impair the associational function of the brain cells that immunity to fear is established. Animals whose natural defense is muscular exertion, among which is man, may have their dischargeable

nervous energy used up by fear alone, by trauma alone, but most effectively by the combination of both. What is the mechanism of this discharge of energy? It is the adequate stimulus of the noci-ceptors — the electric buttons — and the physiologic response for the purpose of self-preservation. According to Sherrington, the nervous system responds in action as a whole and to but one stimulus at a time. The integration of the individual as a whole occurs not alone in injury and fear, but also, though not so strong, under other phylogenetic associations, such as the chase and procreation. When adequate stimuli are repeated in such a rhythm that the new stimulus is received before the effect of the previous one has worn off, a higher maximum is reached than is possible under a single stimulus, however powerful.

Sexual receptors are implanted into the body by natural selection, and the adequate stimuli excite the nerve muscular reactions of conjugation in a manner analogous to the action of the adequate stimulus of the noci-ceptors. The specific response of either the sexual receptors or the noci-ceptors is at the expense of the total amount of nervous energy available at the moment. Likewise, daily labor, which, in the language of evolution, is the chase, expends nervous energy. However, under the dominance of fear or injury the integration is most nearly absolute and probably every expenditure of nervous energy not required for efforts at self-preservation is arrested; hence fear and injury drain the cup to the dregs. This is the potential difference between fear and desire, between injury and conjugation.

What is the practical application of this? In operative surgery there is introduced a new principle, which

removes from surgery much of the immediate risk from its trauma by establishing *anoci-association;* it places on a physical basis certain of the phenomena of fear; it explains to us the physical basis for the impairment of the entire individual under worry or misfortune; the daily noci-associations of the individual as a social unit; or a noci-influence of a part of the body; on the other hand, it explains the power of therapeutic suggestion and other influences which serve for the time to change the noci-integration, the physical basis for the difference between hope and despair; it explains some of the phenomena of Graves' disease, of sexual neurasthenia; possibly of hay fever and the genesis of the common cold, the principle is probably equally applicable to the acute infections whose chemical noci-association gives rise to many of the phenomena of the disease and explains their cure by natural immunity and by vaccines; it should teach us to view our patients as a whole; and especially should it teach the surgeon gentleness. It should teach us that there is something more in surgery than mechanics; and something more in medicine than physical diagnosis and drugs.

Conclusion.

The brain cells have existed during eons of time and amid the vicissitudes of change with perhaps less alteration than the crust of the earth. Whether lodged in man or in the lower animals, they are related to and obey the same general biological laws, thus binding them, that is, ourselves, to the entire past and perform their function on the law of phylogenetic association.

So long have we directed our attention upon tumors,

infections and injuries that we have not sufficiently considered the vital force itself. We have viewed each anatomical and pathologic part as an entity, and man as an isolated phenomenon in nature. May we not find in the law of adaptation under natural selection, and the law of phylogenetic association, the master key that will open to us the explanation of many of the pathologic phenomena as they have already explained many normal phenomena?

And may medicine not correlate the pathologic phenomena of the sick man with the forces of evolution, as the naturalists have correlated the phenomena of the sound man, — and disease as well as health be given its evolutionary setting?