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Beaumont Foundation Lectures

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PREFACE

The Twelfth Series of Beaumont Foundation Lectures commemorates the one hundredth anniversary of the publication of William Beaumont's classic, "Experiments and Observations on the Gastric Juice and the Physiology of Digestion." It represents the present day concept of that pioneer physiologist's striking studies as enunciated by Dr. Walter B. Cannon, distinguished teacher and scholar, in his own right a pioneer investigator in the great fundamental branch of medicine, physiology.

Each of the three lectures has been built around an important phase of Beaumont's epoch-making observations. The first of these deals with "Thirst and Hunger"; the second with "The Important Relations of Digestion and Health"; and the third with "Digestive Disturbances Produced by Pain and Emotional Excitement." A broad terrain in the realm of physiological science is capably covered and a wealth of useful material is presented.

The Lectureship Foundation Committee of the Wayne County Medical Society commends to the reader a careful perusal of this valuable and practical work.

(Signed) W. S. Reveno, M.D.
For the Committee.

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SOME MODERN EXTENSIONS OF BEAUMONT'S STUDIES ON ALEXIS ST. MARTIN

Chapter I

Thirst and Hunger

IN 1929 the thirteenth International Congress of Physiology was held in Boston. The hosts on that occasion were the members of the Federation of American Societies for Experimental Biology, including physiologists, biochemists, pharmacologists and experimental pathologists; and the members of the Congress who came from abroad included eminent investigators from many countries in all parts of the world. When a Congress meets in any country it is customary for the members from that country to select one of their countrymen, who has been an outstanding contributor to the physiological aspects of science, to be commemorated in a medal. In anticipation of the Boston meeting various non-living Americans who had contributed to physiology were considered for that honor. After discussing all the men who were proposed, the Committee having the matter in charge finally selected Dr. William Beaumont, who, in Osler's phrase, was "the pioneer American physiologist." This selection met universal approval. The reason for unanimity of the choice was, I believe, a basic feeling that Dr. Beaumont singularly typified American character. By the accident which opened the stomach of Alexis St. Martin, Beaumont was presented with an unusual opportunity to study the processes of gastric digestion. To be sure, such accidents had occurred in the past but no one had seized the chance thus offered to carry on systematic studies. In Beaumont's case, however, the occasion and the investigator met, and the occasion was seized with intelligence and utilized with the utmost interest and persistence. Working in a backwoods army post, under the most unfavorable conditions, without laboratory aids, with no journals or other literature to consult, with no associates to encourage him and to help him create an atmosphere for research, Beaumont for long periods conducted careful studies on his patient. They exemplified admirable independence and resourcefulness. He recorded his observations in the common language, transparent in its devotion to telling the truth as he saw it. Again and again he had to persuade and cajole the "fistulous Alexis" in order to be able to continue the investigations. Just one hundred years ago, in 1833, he published his classical book entitled, "Experiments and Observations on the Gastric Juice and the Physiology of Digestion." That was not, however, the end of his efforts. Twenty years later, in 1853, he tried again, after many futile attempts, to obtain the cooperation of St. Martin. In October of that year, he wrote to his cousin with characteristic modesty, "I must retrieve my past ignorance, imbecility and professional remissness of a quarter of a century, or more, by double diligence, intense study and untiring application of soul and body to the subject before I die." It was the seizing of the rare chance, the independence of judgment, the ready use of simple methods, the persistent and scrupulous care evident in the studies which Alexis St. Martin made possible, the repeated conquest of difficulties in spite of discouragements, and the clear and direct reporting of observed facts in a field where Beaumont was a pioneer, that made him the investigator whom American physiologists admired and whom they with pride memorialized in a medal.

The selection of Beaumont as a typical American investigator was one which foreign guests at the International Congress could appreciate. Beaumont's studies were known throughout the world. The method which he by chance made use of was, within a few years after his book appeared, applied in studies of lower animals by the great French physiologist, Claude Bernard, and later by many others. Much later the method was used also by the renowned Russian physiologist, Pavlov, in his classical studies of the digestive process, for which, in 1904, he received the Nobel Prize. The backwoods physiologist of one hundred years ago thus received high honor, much greater honor than he could ever have anticipated, from physiological investigators at one of their great triennial meetings.

When I was asked to give the Beaumont Lectures before the Wayne County Medical

Society on this 100th anniversary of the publication of Beaumont's classic, I welcomed the invitation with pleasure and interest. The reasons for that satisfaction are two. It happens that my own life and my early interests in research were in a rather special way related to the life and labors of Dr. Beaumont himself. For about two years he was stationed at Fort Crawford, an outpost set up against the Indians at Prairie du Chien, Wisconsin—then in Michigan Territory. Some of his most important studies on St. Martin were carried on there during the years 1829-31. About forty years later my father and mother were residents of Prairie du Chien, and it happened that I was then born in that small settlement where Beaumont had pursued his researches on gastric digestion. Years afterwards I, too, undertook an investigation of digestive functions. In 1896, when I was a first-year medical student, Dr. Henry P. Bowditch, Professor of Physiology at the Harvard Medical School, suggested that we use the newly developed X-rays to study the phenomena of swallowing. I accepted the suggestion, and in the autumn of that year began observations on the movement of food through the esophagus as revealed by the then very mysterious and miraculous rays. During the holiday week the last of December, 1896, we demonstrated the movement of material through the neck of a goose. The bird was shut tightly in a box through the top of which the neck protruded. A high cardboard collar fixed above the box to hold the neck straight gave the goose a most absurd and pompous air. Such were the beginnings of the use of X-rays in tracing the processes of digestion. Soon we were making use of subnitrate of bismuth as an opaque powder mixed with the food to cause it to cast a shadow on a fluorescent screen. The food that was swallowed by dogs and cats, whose movements of deglutition were being examined, gathered in their stomachs. This accumulation naturally aroused interest in what could be seen of gastric peristalsis and the emptying of the stomach into the intestine. The passage of food into the intestine led to scrutiny of the processes taking place there. Thus, step by step, the progress of food through the alimentary tract was followed. Subsequently, observations were made on the rate of passage of different foodstuffs through different parts of the tract, the effects of the temperature of the food on its treatment, the relation of an acid or an alkaline reaction to its discharge from the stomach, the influence of dilution, and many other conditions which need not now be mentioned. Suffice it to say that the new method has given the opportunity, as Haggard has remarked, for every physician to be a William Beaumont and his patient an Alexis St. Martin, because now it is possible by means of the roentgen rays, as everyone is aware, to examine readily in man the activities of the gastric wall, the changing contour as disease may influence it, and the effects on digestion of many factors that were first observed in lower animals.

The work on the physiology of the gastro-intestinal tract which I had the privilege of beginning thirty-six years ago was summarized in a book published about twenty-one years ago under the title, "The Mechanical Factors of Digestion." Since that time I have not been engaged directly in researches on alimentary functions. Other interests, however, that have occupied my attention during the past twenty-one years, have been the outgrowth of the earlier studies, and they have significant bearings on the activities of the digestive organs. It has seemed to me, therefore, quite in consonance with the spirit of this occasion to consider some of these more recent interests in relation to the observations which Beaumont recorded. Among these later interests are those concerned with the nature of thirst and of hunger, the influence of general bodily conditions on digestion, and the effects of emotional excitement in the organism.

Although the record which Beaumont left us is in the main a direct descriptive account of observations which he made on St. Martin, he occasionally summarized his experience and drew conclusions therefrom. Furthermore, he expressed certain opinions regarding the nature of processes which he could not fully determine by observational methods. Among the opinions were those included in a brief chapter entitled "Of Hunger and Thirst." I propose that we examine today Beaumont's views on these subjects and some of the more recent developments which modify those views.

First let us take up thirst. In a brief consideration of thirst Beaumont quotes Magendie, then probably the foremost physiologist in the world, as saying, "Thirst is an internal sensation, an instinctive sentiment"; "the result of organization and does not admit of any explanation." With characteristic independence Beaumont utterly rejected the limitation which Magendie had laid down. He said, "Thirst is no more an 'instinctive sentiment' than any other sensation of the economy; to say that it is the 'result of organization' gives no explanation, amounts to nothing, and is certainly, to say the least, a very unsatisfactory way of disposing of the question." Beaumont declared that thirst is a sensation arising from the mouth and fauces, a feeling of dryness due to evaporation of moisture from the surfaces of those regions because the passage of the respired air took up the moisture at a rate faster than it could be supplied.

He further suggested that the failure of a secretion adequate for keeping the surfaces of the pharynx moist was due to a viscid state of the blood resulting from an inadequate water supply. Modern research has not supported this explanation of the nature of thirst, for careful studies of the blood have shown that even after several days of lack of water the physical state of the blood is altered to only a minor degree.

Although the theory of thirst as a general sensation was supported by as great a physiologist as Claude Bernard, recent evidence, I think, definitely confirms Beaumont's view that it has a local source in the mouth and pharynx. The main features of this evidence are as follows: Persons suffering from severe thirst because of great losses of water through the kidneys, as in diabetes insipidus, are relieved when the sensitiveness of the nerve endings at the back of the mouth is destroyed by painting the region with cocaine. Moreover, sipping a small amount of water and temporarily moving it about in the mouth will stop the sensation. Also, holding in the mouth a substance which causes a secretion of saliva —a bit of lemon, for instance—will lessen thirst. Not one of these procedures supplies water to the body and yet the distress is mitigated. Since the thickening of the blood cannot explain the local dryness, as Beaumont suggested, some other explanation must be sought which, when the body requires water, would cause the mouth to become dry. This arrangement might reasonably be found only in animals which are continuously and repeatedly losing water, and which, therefore, must have repeated renewal of the water supply in order to maintain a normal condition.

Clues which led to the explanation of thirst were found in comparing the characteristics of water-inhabiting vertebrates with those that are strictly inhabitants of the air. Fish, for example, live in water, and, having a constant stream of water moving through the mouth, they probably never suffer from thirst. The conditions are quite different in the air-inhabiting forms. There is no longer a water current to keep the mouth moist. Instead, there has been added to the structures of the head a nasal chamber through which an air current passes. This current crosses the pharynx to reach the windpipe or trachea. The lining of the nasal chamber and the trachea is well provided with cells which secrete a mucous fluid. On the other hand, the lining of the back of the mouth and the pharynx consists of flattened epithelium having few secreting cells. The air which passes to and fro crosses this ancient water course and therefore tends to dry the region. Prolonged speaking, singing or smoking, which deprives the pharynx of the advantage of previously moistened air, because the air is drawn mainly through the mouth and not through the nose, is especially favorable to drying the mucous membrane at the crossing. The sensation of dryness and stickiness in this area, as Beaumont noted, is recognized as thirst.

Why, then, does not the mucous membrane at the back of the mouth always feel dry and sticky? And why does it feel so, particularly, when the body is in need of water? Again, comparison of water-inhabiting animals with air-inhabiting animals offers a suggestive clue. The vertebrates which live in water do not possess buccal glands, whereas those which live in air have such glands, and they are newly developed features associated with the new type of environment. In the higher air-inhabiting forms the buccal glands have become evolved into the well-known salivary glands. Note especially the significant fact that the saliva which they produce has a water content varying between 97 and 99 per cent. Normally saliva assures a moist lining of the buccal cavity. The theory which these glands suggested was that when water is needed in the body the salivary glands are unfavorably affected by the deficient general water supply. If they do not have water to utilize for secretion they are unable to perform their function of keeping the mouth and pharynx moist. This region, therefore, becomes dry, and thus the sensation of thirst arises. This theory, which I put forth about fifteen years ago, has now a considerable body of evidence to support it. In the main the evidence is derived from observations on a lessened salivary flow and the appearance of thirst when the water content of the body is reduced, or on the appearance of thirst if the mouth becomes dry, even though the body is not dehydrated. Let us consider briefly these observations.

In one of the first experiments I found that chewing of a tasteless gum for five minutes would result repeatedly in a fairly uniform amount of saliva. If no water is taken for many hours, however, there is after a time a gradual diminution in the amount of saliva produced in consequence of the standard period of mastication. In my experience, deprivation of water for twenty hours resulted in the reduction of the output of saliva by approximately 50 per cent. This observation has recently been confirmed by Winsor, who recorded the reduction of the salivary output to one-sixth its normal amount seventy hours after his last drink. My colleague, Dr. Gregersen, has likewise confirmed the observation. A few minutes after a drink of water the salivary output was restored in all cases nearly to normal. Associated with the diminished secretion of saliva there was a definite sensation of thirst—a sensation which disappeared as soon as the supply of saliva was restored. This coincident association of bodily need for water, diminished flow of saliva, and the sensation of thirst, strongly supports the view that the deficient functioning of the salivary glands signals the bodily need by causing the unpleasant sensation.

Again, it was found that the output of saliva can be greatly reduced by abundant sweating. When conditions are established to produce that effect, the standard mastication results in a greatly reduced output of saliva. This is associated with a noteworthy dryness of the mouth and an unpleasant thirstiness which can be rapidly abolished by the drinking of water.

Furthermore, the subcutaneous injection of the drug atropine caused, in my experience, a reduction of the salivary output, in consequence of mastication for the standard period, falling to approximately *one-fourteenth* of its former amount. There was, of course, no noteworthy loss of water from the body. Nevertheless, all of the feelings of ordinary thirst were present.

Quite significant is the evidence that there is a well-established reflex secretion of saliva after the mouth becomes slightly dry. One need only breathe through the mouth for about five minutes to demonstrate that first the moving air gradually dries the buccal surface. As the surface becomes dry, saliva is poured out in an amount which may be greater than that obtained by chewing. The presence of this reflex indicates that salivary glands have as one of their special functions the moistening of the mouth.

We are all probably acquainted, from personal experience, with another important fact,—the appearance of thirst as a consequence of fright and the attendant checking of salivary secretion. There are interesting records of persons who, confronted by terrifying situations, have felt intensely the sensation of thirst. Indeed, this fact was used in the old ordeal of rice in which chewing dry rice and later putting it forth from the mouth were required in order to determine the guilty party in a group of suspects. It was assumed that the one who had most reason to be fearful of the result would be less able to muster the saliva necessary to moisten the rice. Under these circumstances, the intense and distressing sensation of thirst is not associated with any real lack of fluid in the body but results from the local condition in the mouth.

In criticism of the theory I am expounding, Montgomery has recently reported that after removal of the salivary glands from dogs the animals, fed moist food, did not take any more water than before the operation. Gregersen and I have shown, however, that such is not the case if the animals are exposed to conditions which tend to dry the buccal mucous membrane. If dogs deprived of the function of their salivary glands are placed in a warm room where they exhibit panting, the water intake may be increased much more than 100 per cent over their normal intake. Under conditions which make the mouth dry, therefore, a deficient salivary flow evidently causes thirst and an increased water intake, even in the absence of actual bodily dehydration.

Within the last few months Gregersen has shown that, when the time of drinking and the amount of water drunk are registered graphically, the water intake of dogs occurs almost solely within the first few hours after feeding, regardless of the time when food is given. If no food is given for twenty-four hours the usual amount that is drunk is reduced to one-fourth the normal or less. Furthermore, if the giving of water is delayed for some time after feeding, the twenty-four hour intake is ordinarily much less than when water is given freely through the period immediately after the feeding. These interesting observations are reasonably explained by the loss of water from the body into the contents of the digestive canal by action of the digestive glands. As Beaumont showed, there is a large secretion of gastric juice into the stomach contents. To this must be added the water which acts as a vehicle for the ferments from the pancreas, also the water in the bile and that in the *succus entericus*. Of course some of this water goes back into the body as food is being absorbed. As the food passes through the alimentary tract, however, it is abundantly mixed with fluid, which renders the passage easy and which serves as a medium in which the chemical changes of digestion can take place. All the water that is contributed to this mixture is as if actualy lost to the organism. In unpublished studies Gregersen has shown that although there is no considerable thickening of the blood, the blood volume is very much reduced by the water losses which occur because of the digestive secretions. Under these circumstances, again, the salivary glands are deprived of the main constituent of their product and therefore they are unable to keep satisfactorily moist the mucous membranes. Thus is explained the behavior of the dogs in the few hours after eating when they drink abundantly. Thus is explained also their failure to drink if they have not been fed. And thus, also, is explained their failure to drink abundantly if there is sufficient delay in giving them water after a meal, for the digestive juices which have been poured out have then been restored to the body again, and the need for water is no longer present.

Naturally, in our ordinary eating habits we take water with food as we eat. This water is soon absorbed after its passage through the stomach and serves to compensate for the loss of water from the body in the digestive secretions which are poured out as digestion continues after the meal is over. Ordinarily, therefore, we do not experience the postprandial thirst which was manifested by Gregersen's dogs under experimental conditions. Careful observation reveals that usually after a large meal there is a relatively small discharge of water from the body through the kidneys. The reason for that fact becomes clear on the basis of Gregersen's observations,—the body is using water in the digestive process. Only when that process has been completed, and the valuable materials of the food have been absorbed, and the waste has been carried to the colon, is the water restored to the body in amounts which make an excess. Under these circumstances, the organism gets rid of the excess by kidney action.

The evidence which we have just surveyed offers an alternative explanation of the experiments which have been adduced to support the theory that thirst is a general sensation. These experiments in the main consisted of the introduction of water under the skin or into a blood vessel or by way of the intestines (i.e., not through the mouth), and then observing that the sensation of thirst and the desire for taking water disappeared. Obviously, however, just such procedures provide the water supply which allows the salivary glands to operate. The mouth which has become dry because of their failure to operate properly is now moistened again and the sensation of thirst naturally disappears. Its disappearance does not result directly from a satisfaction of a general bodily need but indirectly from the moistening of the mucous membrane of the mouth and pharynx.

We see, therefore, that although Beaumont was right in attributing thirst to a local condition in the mouth and although his bold challenge to the eminent physiologist, Magendie, who had declared that thirst "does not admit of any explanation," was wholly pertinent, we cannot give the same explanation of the phenomenon of thirst which he gave. Instead of assuming an increased viscosity of the blood as a consequence of water lack, we find a reduced blood volume and an attendant reduction of the flow of saliva. That in turn fails to keep moist the mouth and pharynx, and thirst results. Thus the salivary glands act as sentinels to warn against bodily dehydration.

Now let us turn to a consideration of hunger. In the section of his book, "Of Hunger and Thirst," already referred to, Beaumont argued in a very able and self-reliant manner regarding hunger as a sensation. He declared, with reference to the statement that hunger is produced by action of the nervous system and has no other seat than that system, "I cannot perceive that such explanations bring the mind to any satisfactory understanding of the subject. In such a broad proposition it is difficult to ascertain the exact meaning. If the design is to convey the impression that hunger has no 'local habitation'; that it is an impression affecting all the nerves of the system in the same manner, then the sensation would be as likely to be referred to one organ as another." He furthermore argued against certain explanations of the local source of the hunger pang. It was not due to friction of the internal coats of the stomach for three different reasons which he brought out, nor due to irritation of a quantity of gastric juice in the stomach, nor to the "energetic state of the gastric nerves" as had been suggested, nor to the "foresight of the vital principle," which phrase Beaumont declared "means anything, everything or nothing, according to the construction which each one may put upon it." His bold and downright characterization of these views gives relish even as one reads his words today. The explanations, he declared, "are mere sounds and words which convey a tacit acknowledgment of their author's ignorance."

Beaumont's own view of hunger was that it was "produced by a distension of the gastric vessels, or that apparatus, whether vascular or glandular, which secretes the gastric juice." He reasoned that the sensation must have its source in the stomach itself and that the sensation would vary according to different degrees of supposed distension—the greater the distension the more acute the pang. This argument was based largely on the analogy of pain arising from distension of blood vessels in acute inflammation. He cited in support of the argument that the application of food to the internal coat of the stomach results in an immediate throwing out of a quantity of fluid which mixes with the food. Associated with this discharge of secretion was quiescence and relief from the unpleasant hunger pang. He assumed that during the period when the stomach had no food within it, and when therefore no secretion was occurring, large amounts of the gastric juice must be contained in the appropriate vessels ready to be poured forth.

The feature of hunger which, it seems to me, Beaumont overlooked was its intermittent or recurrent character. Careful observation reveals that hunger occurs in periods; that for a moment it may be present, then it is absent, and then a moment later it is present again. Or, it may work up to a climax of disagreeable feeling, and then may totally disappear, only to recur once more in a gradually developing pang. Such observations on hunger I had made as early as 1905. Interestingly enough the first intimation that hunger is due to contractions of the stomach came during a research on the auscultation of abdominal sounds. The disappearance of the recurrent hunger pangs was commonly associated with a rather loud gurgling noise as heard through the stethoscope. Apparently Beaumont made similar observations. In experiment 65 in his third series, he reports that the introduction of 3.5 drachms of lean, boiled beef through St. Martin's fistula caused an immediate disappearance of the sensation of hunger, and therewith "stopped the borborygmus, or croaking noise, caused by the motion of air in the stomach and intestines peculiar to him since the wound, and almost always observed when the stomach is empty." Beaumont drew the conclusion that this experiment proves that the sense of hunger resides in the stomach. He did not go further, however, and infer that the noise which was heard could only be due to a vibration of air forced by muscular contraction through a narrow orifice.

The time and opportunity for securing evidence as to the cause of the periodic recurrences of the hunger pangs, which I had noted in 1905, did not arise until about 1910. At that time one of my medical students, Arthur Washburn, expressed a desire to carry on investigations in the laboratory, and since he had the unusual ability of regurgitating his gastric contents at will, I proposed to him that we undertake a study of the nature of hunger, and suggested that he become accustomed to having a tube in his esophagus. He took this advice and for days serenely carried on his work in the laboratory with a tube reaching down to his stomach and prevented from going further by a firm grip on its upper end in his clenched teeth. When he had become thoroughly accustomed to this strange condition, we fastened a balloon on the end of the tube and introduced the balloon into the stomach. Then Mr. Washburn, who is now a practicing physician in New York City, would come to the laboratory without breakfast and sit with his back to a recording apparatus ready to press a key whenever he felt hungry. The interesting fact soon developed that quite apart from any contractions of the abdominal wall there were powerful contractions of the stomach which lasted approximately a half-minute and recurred after an inactive interval of about a minute, and that the sensation of hunger was associated with the acme of these contractions. Thus, evidence was adduced that the hunger pangs themselves were due to a cramp-like tightening of the smooth muscle of the gastric wall.

The evidence for associating hunger pangs with gastric contractions was first reported in a lecture before the Harvey Society in New York City in December, 1911. The full report was published in March, 1912. At about that time there appeared in the laboratory of Professor A. J. Carlson, the Chicago physiologist, a real second Alexis St. Martin, a man with a fistula through which it was possible to make studies of the gastric digestive processes quite as Beaumont had done so many years before. This favorable accident made it possible for Carlson to work on the phenomena of hunger in a highly convenient manner. Since at that time I was much interested in the effects of emotions on the body, I turned to that field, and left further investigations of the nature of hunger wholly to Carlson and his students.

In a series of interesting researches on human beings, some of whom, like Washburn, recorded gastric contractions through a tube in the esophagus, and also in studies on various kinds of lower animals, Carlson and his collaborators have examined the phenomena of hunger in health and disease, and have not only confirmed the observations which we had made but have brought out many new aspects of the hunger pangs and the relation of gastric contractions to them. For example, we had observed only the separate rhythmic recurrences of the powerful activity of the gastric wall. They were able to prove that in addition the phenomenon of hunger usually begins with occasional weak contractions, that these become gradually more vigorous and appear at shorter intervals until a supreme degree of activity is reached which may culminate in an actual spasm of the smooth muscle. Both the single contraction and the spasm are associated with the typical unpleasant ache, or pang, or gnawing sensation which has long been recognized as the experience of hunger. After the acme of activity has been reached, the stomach usually relaxes and remains inactive for a period, whereupon it starts again with occasional weak contractions, and the cycle of increasing activity followed by quiescence is again repeated. Carlson's second Alexis St. Martin reported that distending the stomach by the balloon or rubbing the mucous lining of the stomach with a smooth object did not cause the sensation of hunger unless these procedures caused contractions. It is definitely the contraction of the gastric muscle, therefore, that brings about the hunger pang.

By simultaneous observations on the pressure changes in the stomach (as recorded from an intragastric balloon during the experience of hunger) and on the gastric contractions (as examined by means of the roentgen rays) Rogers and Martin have found that there are two types of activity in the stomach during the hunger pang. At the height of the pang the lower portion of the stomach may be so strongly contracted that the cavity in that region is completely obliterated. In addition, there may be unusually powerful gastric peristalsis at such a rate that the second wave appears before the first one has gone.

Carlson has studied also with care the conditions which might influence the hunger contractions. For example, sleep does not interfere with them, although they may interfere with sleep and thereby produce restlessness. The contractions are stopped by chewing, and they may be temporarily inhibited by swallowing, a fact which I had noted in 1905. As I shall explain in my third lecture, strong emotional states abolish all digestive activities in the alimentary tract. It is interesting to note that such states likewise abolish the gastric contractions associated with hunger. They are weakened and may be completely checked by smoking; and apparently in this respect the efficacy depends predominantly upon the "strength" of the tobacco. The direct introduction of alcoholic beverages—undiluted beer and wines and 10 per cent alcohol—into the stomach through the gastric fistula causes cessation of the hunger contractions, and also lessening of the tonus of the empty stomach. Very vigorous muscular exercise also inhibits the periodic waves of hunger, but after the inhibition they are likely to occur with greater intensity than before. We have all heard of the advice to tighten the belt, when hunger pangs are intense, in order to abolish them. Tightening of the belt does, indeed, lead to a stoppage of the hunger contractions if they are weak or of moderate strength. The stoppage then may be partial or complete but it lasts only a short time, from 5 to 15 minutes, whereupon they reappear despite continued pressure of the belt.

In almost every audience there are found a few persons who will testify that they have never experienced the pangs of hunger. It is known, furthermore, that although the hunger pangs cease to be disturbing after the first few days of fasting, the hunger contractions still continue. These two facts appear to minimize the importance of hunger contractions as a source of hunger pangs. They are not, however, cogent arguments for the conclusion that the contractions are not the source of the pangs, because many circumstances may prevent stimuli from having their usual effect. A ticking clock, for example, may not produce the sensation of ticking because other stimuli are simultaneously affecting the nervous system, or because, for instance, the nervous system may be dulled by sleep. That the ticking is not heard at times does not prove that it does not produce the sensation when it is heard. Recently Christensen has reported an inability to find a relation between the presence or strength of gastric contractions and the presence or intensity of hunger sensation. He did indeed find that in conditions of gastric disease typical "hunger pains" were associated with vigorous contractions of the empty or nearly empty stomach. But even under these conditions strong contractions were recorded that were not associated with hunger pangs. This, however, is negative evidence. It seems to me that it can have little force in view of the consideration that other stimuli may influence attention and thereby lessen the influence of the hunger contractions, and in view, also, of the positive testimony of numerous investigators who, since the time when Washburn and I first studied the phenomenon, have found that the pangs of hunger have their immediate source in strong contractions of the gastric musculature.

The interesting problem arises as to what induces the stomach while empty to contract with a much greater vigor than when ordinary peristalsis is coursing over the wall during the digestion of a large meal. The opinion has been expressed that the general bodily need of nutriment affects a part of the brain, that thereupon this serves as a stimulus to arouse gastric contractions, and that these then produce hunger pangs. Carlson has shown, however, that the typical contractions of the empty stomach occur when that organ is completely isolated from the brain and spinal cord, though at somewhat longer intervals than in normal animals. Again, it is known that the elective source of energy for muscular activity is carbohydrate food—glycogen, or sugar. It seemed possible that a deficiency of this energy-yielding material might be signalized by excessive shortening of the smooth muscle of the stomach. Bulatao and Carlson observed that if the sugar concentration of the blood was reduced about 25 per cent by the use of insulin, the hunger contractions became more intense—an observation which had been noted subjectively in human beings who had received an overdose of insulin. That this effect is caused by the lowering of blood sugar and not by insulin was proved by the Belgian investigators, La Barre and Destrée. They followed the gradual drop of the glycemic level after removal of the liver and found that gastric contractions began to appear when the sugar percentage reached about 75 mg. per cent (i.e., about 25 per cent below normal), and that within limits the intensity and frequency increased rapidly as the percentage fell to lower levels. Bulatao and Carlson reported that on injection of sugar into the blood stream the hunger contractions were abolished. Although this evidence is suggestive, it cannot be regarded as definite proof that the hunger contractions are due to lack of circulating sugar, for the sugar used to abolish the contractions was excessive both in amount and concentration as compared with normal blood sugar. Moreover, if a pyloric pouch or accessory stomach is made by isolating a part of that organ from its main body, the activity of the pouch is not affected by insulin nor by intravenous injections of glucose. And furthermore, Quigley and Hallaran have observed that the *spontaneous hunger contractions* of normal or vagotomized dogs are not modified by intravenously infused glucose in a wide range of doses. The discrepancy between the behavior of the gastric side-pouch and the main body of the stomach, just mentioned, points to a local automatism as the primary factor rather than to the condition of the blood, for the character of the blood flowing to the main stomach is necessarily the same. The problem as to the cause of the contractions, therefore, still remains unsettled.

Although the evidence is clear, therefore, that hunger contractions can occur in the absence of nervous government from the brain and spinal cord, there is strong testimony indicating that conditions in the brain may so affect the vagus nerve as to cause a large augmentation of the hunger contractions and consequently the hunger pangs. This evidence has come chiefly from the experiments by La Barre. He produced an experimental arrangement whereby the head of Dog B was connected with its body only by the vagus nerves; then he perfused this isolated head of Dog B with the blood of Dog A, which was allowed to run into the head and back again to the body of A. If now dog A, which is the donor, is given insulin to such a degree as to produce a definite hypoglycemia, there results as a consequence of the passage of the hypoglycemic blood from A into the head of B an increase of B's hunger contractions. Note again that the only connection between the head of Dog B and its stomach is through the vagus nerves. This experiment definitely shows that the impulses to increase gastric activity originated in the brain, because the blood supply to the brain was low in its sugar content and was transmitted to the stomach by way of the vagi. Further proof that the vagus nerves mediated the impulses of the brain, in these experiments, was obtained by noting that the hunger contractions ceased on the injection of atropine, the effect of which in blocking vagal impulses is well known. Similar observations have been made on human beings by Quigley, Johnson and Solomon.

Just as thirst is an indication of the need of water in the body and the capacity of the body to receive water, so hunger is a stimulus driving us to the taking of food. It is evident now that we have in our hands a means by which hunger pangs can be stimulated at will. In case of chronic inanition and absence of desire for food, it is only necessary to give a sufficient amount of insulin to reduce the blood sugar, whereupon the accessory vagus influence on gastric contractions is brought into play, and hunger pangs are produced which lead to the taking of food. It is probable also that insulin serves as a means of utilizing more effectively the food which is taken. Recent reports of the use of this strategy in persons who have poor appetites, eat little and are thin indicate that it is highly effective as a means of increasing the bodily stores.

Our behavior may be directed both by the desire of getting rid of a disturbing stimulus and by the desire to prolong or renew an agreeable stimulus. Hunger and thirst belong to the former category. Also in this category are the asphyxia of air-hunger, the discomfort of fatigue, and the unpleasantness of confinement or physical restraint. Each of these states is associated with an impulsive factor. Each one more or less vigorously spurs us on or drives us to action. Each may be so disturbing as to force us when afflicted by it to seek relief from intolerable annoyance or distress. On the other hand, experience may condition behavior by showing us that the taking of food, drink or exercise is accompanied by anticipated pleasure. It is thus that appetites are established for the repetition of these experiences; and when we are beset by an appetite we are tempted, not driven, to action—we seek satisfaction, not relief. The two motivating agencies, the pang and the pleasure, may be closely mingled. For example, when relief from the pang is found, the appetite may simultaneously be satisfied. In most of our experience as civilized human beings, appetite gives us an assurance of the supplies of food and water. If, however, the requirements of the body are not met in this mild and incidental manner, hunger and thirst arise as powerful, persistent and tormenting stimuli which imperiously demand the taking of food and drink before they will cease their goading.

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Chapter II

Important Relations of Digestion and Health

THE ancient physicians regarded the heart, the lungs and the brain as the tripod of life, for if any one of these organs fails the vital activities must necessarily fail. It has seemed to me that a proper extension of this idea would make the basis on which the tripod rests the normal functioning of the digestive tract. By means of the digestive processes the energy-yielding material, which is absolutely essential for the functioning of the body, is made serviceable, and when they fail or are deficient in their services all of the rest of the organism is involved. The digestive organs, however, do not constitute an isolated system but are one of a group of related systems. They serve the other systems and are in turn served by them. Thus it is true that not only do the digestive organs suffer when the body suffers but the body suffers in turn when they are disordered.

The most important of the relations of the digestive tract to other systems of the body is, I think you will admit, the relation to the central nervous system. Through the nerve connections between the gastrointestinal canal and the spinal cord and brain, conditions highly favorable or unfavorable to proper digestion may arise. These connections are provided in the so-called "autonomic nervous system." In order that we may understand clearly its influence on the functions of the digestive organs, it will be well, perhaps, to review briefly some of its characteristics.

As many of you know, the autonomic differs from the cerebrospinal nervous system in being described solely in its outgoing pathways. It innervates striated cardiac muscle, to be sure, but more typically it innervates smooth muscle and glands. It supplies the walls of blood vessels, the bladder, the uterus, the stomach and intestines, the liver, pancreas and salivary glands, the bronchioles—in short, the viscera and the vascular and respiratory channels.

Another important feature in the organization of the autonomic system is the presence in the outgoing pathway of at least one neurone, outside the central nervous axis, that is interposed between the neurones of the central axis and the innervated structure. Further, the cerebrospinal nerves reaching forth to these outlying neurones are divisible into three groups: the cranial and the sacral, arising, as indicated by the terms, from the brain and from the sacral portion of the spinal cord; and the thoracolumbar, arising from the spinal cord between the brachial and sacral enlargements. The last is the sympathetic division, or the true "sympathetic system," as distinguished from the cranial and the sacral, or parasympathetic, divisions. In the sympathetic division the cerebrospinal nerves (the white rami) pass out on either side of the spinal column to a chain of ganglia, extending from the superior cervical ganglion high in the neck to fused ganglia in the pelvis. These ganglia are the seat of the cell bodies of the outlying neurones of this division. The fibers passing out from the ganglia to smooth muscle and glands are called "post-ganglionic fibers." They are widely distributed all over the body, to arterioles, to sweat glands, to hair muscles, to the genito-urinary tract, and to all parts of the alimentary canal and its glandular accessories.

The fibers of the white rami, connecting the central nervous axis with the sympathetic ganglia, are designated "preganglionic fibers." A peculiar feature of the arrangement of these fibers is that they not only reach to the nearest ganglion from their source, but pass through that one to neighboring ganglia up and down the chain, giving off collateral branches in each one. This arrangement of the preganglionic fibers results in an interlacing of their distribution. In any ganglia there may be axones from four or five different segments of the spinal cord; or, to put it differently, axones from any segment of the cord may pass through four or five different ganglia of the sympathetic chain, connecting the ganglia with one another and at the same time distributing to outlying neurones in each one. This mode of organization has two effects; it greatly increases the range of distribution of impulses coming out along any single fiber, and it also provides for diffuse distribution of impulses throughout the organism.

Associated with the sympathetic system is the adrenal medulla which is innervated by nerves from that system. When the sympathetic division is stimuluated, in great excitement, for example, there is a discharge of adrenin from the adrenal medulla into the blood stream. The circulating blood gives adrenin a diffuse distribution. Since this chemical agent has almost everywhere in the body the same effects as sympathetic impulses, it is clear that the arrangement of the sympathetic neurones for diffuse activity is supported by the diffuse distribution of adrenin. We may speak, therefore, of a sympathico-adrenal coöperation, with an activity diffusely effective.

A distinguishing feature of the sacral and cranial divisions of the autonomic system is that the preganglionic fibers of their outflow pass directly to the neighborhood of the organs innervated, or into them, and therefore have a distinct and discriminating rather than a diffuse influence. Thus the third cranial nerve reaches to the eye, the chorda tympani to the submaxillary gland, the vagus to the heart and the stomach, before finding a relay in the outlying neurone. It is usually true also that when representatives of either the cranial or sacral division meet in any organ the representatives of the sympathetic division, they are opposed in action. Thus the sympathetic impulses accelerate the heart, and the vagal impulses (from cranial sources) check or inhibit the heart. Exceptions to this general rule we shall note later.

As we continue our discussion we shall have repeated occasion to refer back to the rôle of the autonomic system in the regulation of the functions of the digestive organs, for these functions, as we all know, are carried on by smooth muscle and glands.

It must not be supposed that the extrinsic nerves connecting the alimentary tract with the central nervous system are essential for its functions. Just as the heart will continue its services as a pump and keep the circulation going although both of its external nervous connections, sympathetic and vagal, have been severed, so likewise the alimentary tract is capable of carrying on its activities without external nervous control. Many years ago Hofmeister and Schutz wrote a rather elaborate paper on the movements of the stomach, excised, removed from the body, and observed in a moist chamber. The peristaltic waves went on in a quite normal fashion. Similarly, in 1906, I reported X-ray observations on the functioning of the gastro-intestinal canal after the vagus nerves and splanchnic branches of the sympathetic division had been severed, so that the stomach and small intestine were deprived of any extrinsic control. If, then, the digestive organs are capable of carrying on their functions in the absence of nervous government, the question arises as to the utility of these nerves. I hope to present evidence to you in this and the next lecture that the rôle of the extrinsic nerves, insofar as the motor activities of the tract are concerned, is that of affecting the "tone" of the smooth muscle of its walls. The word "tone," or "tonus," or "tonicity" is one that is rather loosely employed both by practicing physicians and professional physiologists.

We should understand definitely what we mean when we employ it.

It seems to me that the word "tone" signifies, at least in its unqualified, physiological use, a persistent moderate degree of activity. Thus we speak of vasomotor tone or vascular tone as a continuous control over the blood vessels, of such degree that it can be varied in either direction—the tone can be increased by stimulating a pressor nerve or can be reduced by stimulating the depressor nerve. Likewise, we speak of the vagus nerve as exercising a tonic control over the beat of the heart, keeping the rate steadily, unless disturbed, at an intermediate level between great rapidity and extreme slowness. By increasing the vagal tone the heart is made to beat more slowly; by decreasing the vagal tone it is made to beat more rapidly. When this idea is applied to the control of skeletal muscle it becomes somewhat more precise. We understand by the tone of skeletal muscle the continuous moderate *tension* in which it is held so long as it has its proper nerve supply. This tension makes the difference between the "feel" of a muscle which is normally innervated and one that has lost its nerve connections, or the difference between the feel of the muscles in the living and in the dead body. But the word "tone" may be extended still further and may be applied to the body as a whole. Thus we may speak of the state of health as being a state of tonic well-being. Definitions of health are not satisfactory. Perhaps as good a concept of health as any is that of a state in which, with basal conditions of bodily activity, the functions of various organs essential for existence continue at a moderate rate, and in which the stress of great effort can be met without failure of prompt return to the former status. The basal metabolism, with its attendant slow cardiac and respiratory rate, has familiarized us with this concept. You will recognize that it is similar to the concept of "tone" as a state of persistent moderate activity, in quiet conditions, that can be varied in either direction—increased or decreased. But we have wandered far from our starting point. When I use the word "tone" in describing the effects of the extrinsic nerves of the alimentary canal on its musculature, I shall employ it in its narrower sense of indicating the continuous degree of tension which this musculature is exhibiting. With this explanatory preparation we may proceed to consider the rôle of the extrinsic nerves of the alimentary tract, and in the present lecture, specifically, the vagal and the sacral nerves, as representatives of the parasympathetic divisions.

The two vagus nerves are distributed throughout the alimentary canal from its beginning in the upper esophagus to the end of the small intestine. We shall restrict our interest to the effects which they have on that portion of the tract which is composed of smooth muscle. The literature on the influence of the vagi on the functions of the esophagus, the stomach and the intestines presents us with many confusing results. A great variety of effects have been reported as a consequence of stimulating these nerves at various points in their course. Some of these incongruous results can be explained as a consequence of what may be called "induction coil" physiology. By that I mean that artificial electrical stimuli have been applied to a complex neuromuscular organization and the effects thus produced have been assumed to demonstrate the function of the structure stimulated. The effects are correct enough for the conditions which prevail at the time, but in my opinion they have nothing but suggestive value as to the true physiological service of the impulses which the nerve fibers normally convey. Thus, for example, Veach, in the Harvard Physiological Laboratory, found that when he applied stimuli of low frequencies and intensities to the vagus trunks, they produced contractions in the esophageal and gastric muscle which they innervated; and when he applied high frequencies and intensities quite the opposite effect was produced. Indeed, he was able to stimulate contraction with one vagus nerve and produce inhibition with the other by means of that artificial stimulation. Such evidence must always be checked by direct observation of the rôle played by the nerves under natural conditions, and after removal of their influence. It is this latter sort of evidence which I wish to bring before you. Since the situation was simpler and more decisive in observations made on the lower part of the esophagus, I shall describe the experiments made on that region in some detail. The facts brought out thereby will be applicable to other parts of the alimentary tract.

Almost one hundred years ago Reid declared that severance of the vagus nerves results in a paralysis of the esophagus and a failure of deglutition. This doctrine came down through the decades until fairly recent time. Two important considerations were overlooked by Reid. First, the difference between the immediate effects of vagus section and the later possible recovery, and second, the fact that in many animals the lower half of the thoracic esophagus has a coat of smooth muscle.

In 1907 I had occasion to note that for some time after severance of the vagus nerves there is a total absence of peristalsis in the esophagus, and that this paralyzed state was followed by a gradual and remarkable restoration of function in the part of the tube which is equipped with smooth muscle. Immediately after the operation and for twenty-four hours, at least, thereafter, it is easy to demonstrate complete inaction. By means of the X-rays the food which was forced onward into the gullet by the intact upper portion was seen in one instance to stagnate in the thoracic part for five hours, and in another instance for seven hours after the feeding. As bolus after bolus was swallowed the thoracic esophagus became filled with a distending mass which bulged its walls outward until it had a sack-like form. Continuous observation revealed no sign of activity. In short, as a consequence of removal of vagal influence, the esophagus had utterly lost all muscular tone —it relaxed to the limit without any tensile or contractile reaction. The next day the accumulated mass had disappeared. Now food mixed with subnitrate of bismuth was again given repeatedly. When the thoracic esophagus had been distended to approximately twice its normal diameter (*i.e.*, not so much as on the day before), a constriction of the wall in the lower portion, where smooth muscle was present, occurred and moved towards the stomach. This was followed by other peristaltic constrictions moving downward. Gradually these recurring waves pushed food into the stomach until the amount present was considerably reduced. On the third day the experiment was repeated and then it was found that the esophagus need be only slightly distended before the peristaltic wave started and effectively pushed the mass above it through the cardia.

A review of these observations brings out the fact that an important condition for the arousing of peristaltic activity in the lower esophagus is the stretching of the muscular wall. A slender mass of food spread along the denervated tube may lie for some time unmoved. An addition to the first mass, that causes a stretching of the wall, results in the instant appearance of peristaltic waves. Similarly, after repeated reductions have rendered the strand of food more attenuated, it lies for longer periods unaffected by esophageal contractions. As time elapses after severance of the vagus nerves the smooth muscle of the esophagus becomes more responsive to the presence of contained material, for the material is driven into the stomach with increasing rapidity, and even slender masses are sufficient cause for peristalsis. Apparently the recovery of this functional activity is due to a restoration in some manner of the tone of the smooth muscle—a moderate contraction so that it has a capacity for exhibiting tension when stretched—a capacity ordinarily maintained by vagus influences but gradually developed intrinsically when those influences are lost.

An effect similar to that observed in the esophagus may be observed also in the stomach after severance of the vagus supply. The condition there differs in one important respect, however, for, whereas in the esophagus the vagus control is not opposed by sympathetic control, in the stomach the two sets of nerves, vagi and sympathetic, are both present. In order to determine the function of the vagi alone, therefore, it is necessary to be rid of the sympathetic nerves previously. When this condition has been met, removal of vagal influence results in a marked depression of peristaltic activity. For some hours after the nerves have been severed and the animals thereafter have been fed (by stomach tube), the food may lie in the stomach wholly undisturbed by peristalsis; and often when the peristaltic waves begin under these circumstances and are running at their normal rhythm, they are characterized by being extremely shallow. Sometimes they are hardly visible. At other times they can be seen only near the pylorus. As days pass, these abnormalities largely disappear and thereafter the waves start at the usual time after a meal and have much of their normal vigor. These observations, reported in 1906, have been confirmed by Borchers, who reported that only after five days were the normal conditions fully restored. They have also been confirmed by M'Crea, M'Swiney and Stopford. Although these investigators attributed the dilation and signs of paralysis, with delay of all motor functions immediately after vagus section and recovery only after seven to ten days, as due to "shock"—a term which they do not define—they seem to have overlooked entirely the evidence which had been reported that severance of the vagi leads to the absence of tone in smooth muscle and that only gradually is an intrinsic tone recovered.

The similarity between the effects of vagus section on the stomach and on the esophagus is noteworthy. As we have seen, the immediate effect on the esophagus of cutting these nerves is paralysis. The food stagnates in the tube for hours, distending its walls, but the atonic muscle makes no response. As time passes and the musculature of the esophageal wall recovers the tonic state which the vagi formerly maintained, it simultaneously recovers its capacity to respond to the contents which stretch it, and thereupon effective peristalsis is restored. In the stomach, likewise, there is an extraordinary development of an intrinsic tone after the sympathetic nerves and the vagi have been severed. Under these conditions, the resting stomach of the cat, for example, may contract to a diameter of only 2 cm. or less, a smallness of size almost incredible. When this degree of inherent tonicity has been developed, the conditions provided by the vagi have been restored or perhaps somewhat exceeded, and the stomach is then capable of exhibiting its normal peristaltic waves.

We are now in a position to summarize the outstanding natural functions of the vagus nerves with reference to the smooth muscle of the esophageal and gastric walls. These nerves are not "motor nerves," as is sometimes said, but at proper times they exercise a continuing positive influence, an influence which causes the muscle to exert a tension and which therefore is a condition for rhythmic contractions. If the tonic activity of the vagi is increased the vigor of peristaltic contractions increases. If the nerves are severed muscular tone is temporarily lost, the activities of the tract are for some time in abeyance, and even when peristalsis reappears the rings of contraction are at first shallow. This recovery of peristaltic activity is associated with the development of an intrinsic tonic state in the smooth muscle itself. We may conclude, therefore, that the most important natural function of the vagi is that of setting the muscles in continuous moderate contraction, of making them press on the material which they surround, so that in relation to the gastric contents, for example, the muscles are as if stretched by those contents.

From what I have said regarding the service of the vagus nerves in maintaining tonicity of the gastric musculature I do not wish to be understood as denying the presence in the vagus trunks of fibers which on occasion have an inhibitory action. The vagi must be recognized as compound nerves. In relation to the stomach their chief function, causing in the gastric wall a state of moderate contraction, may produce, while digestion is going on in the organ, a considerable intra-gastric pressure. Suppose, now, that while gastric digestion is in progress one desires to swallow more food. It is clear that if there were no other arrangement the muscles of the esophagus would have to force the food bolus into the stomach against the pressure existing there. It happens, however, that a very beautiful adjustment obviates that necessity. In 1911 Lieb and I found that whenever a swallowing movement occurs the intra-gastric pressure drops gradually almost to zero. The fall starts between 2 and 5 seconds after the larynx is lifted in the act of deglutition, and reaches its lowest point (in the cat) between 6 and 10 seconds after the bolus leaves the mouth. The admirable character of this receptive relaxation of the stomach can be appreciated if we recall that the time required for a bolus to be carried through the cat's esophagus varies between 7 and 10 seconds. Thus whenever a tonic state of the gastric musculature has raised intra-gastric pressure, an automatic mechanism exists for lowering that pressure while the esophagus is pushing new material into the stomach. This reciprocal adjustment between the esophageal muscle and the gastric muscle wholly disappears after the vagus nerves have been severed. These nerves, therefore, not only have fibers for the conveyance of tonic impulses, but also fibers for inhibitory impulses.

The vagus nerves are described as being distributed throughout the small intestine from the pyloric to the ileocecal sphincter. It appears that these nerves exercise on the small gut, as well as on the lower esophagus and stomach, a tonic influence. After complete severance of the splanchnic nerves I observed that the rate of passage of a standard food through the small intestine was much accelerated, whereas after the vagi were cut the passage was slower than usual. This is the result which might have been anticipated if the vagi had been assumed to have the same tonic effect on the musculature of the intestine as on the stomach.

In connection with the extrinsic innervation of the intestine it is of interest to note that Langley has reported that the vagi have a diminishing influence in the course of their distribution along the small intestine. This statement is related in an interesting way to observations which were made in the Harvard Physiological Laboratory in 1914 by Alvarez. He studied the rate of contraction of segments of the small intestine of the rabbit, taken from different parts of its extent. His experiments showed quite clearly that the segments from the duodenum exhibited a much more rapid rhythm than those taken from the lower ileum; roughly the rate varied inversely as the distance from the pylorus. Furthermore, the segments from the upper intestine were less inhibited by adrenalin and recovered from the inhibition more rapidly than those from the lower portions. Later studies by Alvarez have brought out other interesting facts, indicating a descending gradient of activity along the small intestine—a gradient not only in rate of contraction of the excised segments but in carbon dioxide output, in irritability, in tonic contraction and in the brevity of the latent period. I had noticed earlier that the food, after passing out of the pylorus and being churned in the first part of the duodenum, was carried thence, much more rapidly than anywhere else, to distant parts of the gut. It seemed to me that this observation was related to the fact which seems to have been observed by the early anatomists when they gave the term "jejunum" to this part of the small intestine, for if it is more active than other parts it must, of course, rapidly empty itself.

Although the observations made by Alvarez did not involve the functioning of the vagus nerves, because the intestinal segments studied by him were removed from the body, it appears not improbable that any natural capacity of the intestine to act with greater speed at its upper than at its lower end would be favored by the attendant descending gradient of vagal influence mentioned by Langley. This suggestion is supported by the evidence already mentioned that when, after the splanchnics are out of the way, the vagi are cut, the passage of food through the small intestine is greatly delayed.

The large intestine, as previously stated, receives its tonic innervation through the sacral visceral nerves, stimulation of which causes contraction of the colonic wall. The extent of the distribution in man, so far as I am aware, has not yet been determined. In the cat, however, these nerves serve only the distal two-thirds of the colon. The stimulation of the nerves causes an increase in the tone of the mid-region as a first effect. Continued stimulation results in shortening of the strong longitudinal muscular coat of the distal half of the colon, and thereafter a deep contraction of the circular coat which moves downward in a manner characteristic of natural evacuation of the bowel. Section of the nerves results in changes which are typical of lack of tone; the feces accumulate and the contractions of the gut are sluggish and weak. These observations, made by Elliott and Barclay-Smith, were unfortunately not preceded by section of the sympathetic supply and therefore indicate merely that the sacral visceral nerves offer a tonic opposition to the inhibitory sympathetic influences.

The importance of tone for peristalsis, first noted in the esophagus, was clearly confirmed in observations made on the reversed waves of the proximal colon of the cat. If this region is relaxed and inactive, painting the gut at the junction of its first and middle third with barium chloride will cause a tonic constriction to form there. While this circular muscle is in maximal contraction it has no influence on neighboring parts. When it partially relaxes, however, it begins to contract rhythmically, and at each contraction it sends off a peristaltic wave. If the material on either side is of fluid consistency, waves may pass away in both directions. If the material is fluid only on the proximal side, the recurring waves are solely anti-peristaltic, i.e., towards the cecum. The interest of this observation lies in the facts that the sacral visceral nerves establish a tonic state in the middle third of the colon, just where the tonic ring was artificially caused by barium chloride, and that the reversed waves sweeping over the proximal region are dependent on a tonic contraction in that region.

Perhaps a word of warning should be given here to the effect that the reversed peristalsis, observed as a normal phenomenon in lower animals, has not been observed in man. Although in human cases there is clear evidence of a movement of material backward towards the cecum, the actual occurrence of waves to produce this effect has not been seen. The main reason for mentioning the evidence for these natural reversed waves in the cat and dog is to emphasize once more the importance of tonus for the movements of the alimentary canal.

Alvarez has called attention to the possibility of a pathological reversal of the descending gradient in the small intestine. Just as barium chloride solution painted on the colon establishes a center of activity and a source of peristaltic waves, so likewise, he infers, irritation by an inflammatory state, for example, in the lower ileum, may make that region a center of activity and thus reverse the gradient. In such manner Alvarez would account for the evidence that in pathological states there may be actually a passage of the intestinal contents in a direction opposite to the normal.

Related to the tonic state of the colon is the function of defecation. In man the changes which occur in the performance of this function have been studied and described particularly by Hertz, who used the roentgen rays in his examinations. Hertz's tracings show that the entire large intestine below the splenic flexure is normally evacuated in a single act. Thereafter, usually during the next twenty-four hours, waste material accumulates in the distal colon. It first stops at the junction between the pelvic colon and the rectum where an acute angle seems to offer some obstruction to progress. Gradually the pelvic colon fills from this point upwards, and as more material arrives it gathers progressively in the iliac and descending colon. On becoming distended the pelvic colon rises and widens its acute angle with the rectum, thus removing the obstruction to the advancement of the fecal matter. When some of this matter enters the rectum the desire to defecate occurs. The usual performance of the act regularly after breakfast is probably due, at least in part, to stimulation of peristalsis in the colon by taking food—probably a tonic effect—though the muscular activities which attend rising and dressing probably play an additional rôle. If these conditions do not result in the natural "desire to defecate" voluntary contraction of the muscles surrounding the abdominal cavity may cause some feces to enter the rectum and thus evoke the call.

When the call for defecation has come the further performance of the act is commonly attended by increased intra-abdominal pressure, a result of voluntary contraction of the abdominal muscles and the diaphragm. As the diaphragm contracts, the entire transverse colon is pushed downward and the ascending colon and cecum are forced into an almost globular form. Intra-abdominal pressure, as measured in the rectum during this stage, may rise to between four and eight times the normal—i.e., it may be between 100 and 200 mm. of mercury. The pressure causes more feces to enter and distend the rectum and the anal canal. The distension of these parts now arouses reflexes which start strong peristaltic contractions of the colon, continues the tendency to strain the voluntary muscles, and produces relaxation of both anal sphincters. Although, as I have described the process, it involves voluntary factors, we should recognize that such factors are not requisite, for the act can be perfectly performed by animals, man included, with the spinal cord severed.

The relation of tone to the important function of ridding the body of waste from the ingested food lies in the fact that only when there is a tonic shortening of the smooth muscle of the rectum is it stretched. The stretching sets up the reflexes which cause it to contract and empty out the contents. If the lower spinal cord is destroyed or the sacral visceral nerves are severed, feces accumulate and the contractions of the gut are sluggish and weak, at least until there is a recovery of intrinsic tone by the rectal muscles. Now for the moral of this story! Observations on man have shown that, if the call for defecation is not responded to, the rectum may accommodate itself to the presence of fecal accumulation. A feature of this condition may be a lessened sensitiveness of the afferent nerves from the region. Perhaps a more important condition is a lessened tone of the smooth muscle so that the accumulated mass no longer produces the normal stimulus of stretching. In any case, under these circumstances, the call for defecation may disappear. Thus if the signal for emptying the rectum is not promptly obeyed, it may cease to be given. The feces may then remain there for a long period without calling forth sensations, and the efficacy of the reflex may be largely impaired.

What I have said thus far regarding the influence of the vagal and the sacral visceral nerves as representative of the parasympathetic supply of the gastro-intestinal tract may seem only remotely related to the title of this lecture, "Important Relations of Digestion and Health." All that has been said, however, is in fact closely related to it. The reason for confidently making that statement is that the parasympathetic nerves share with the rest of the body in any debilitating illness. For example, while the vagal connections between the alimentary canal and the central nervous system are intact, the asthenia, associated with general infection and characterized by soft toneless skeletal muscles, is associated also with a toneless state of the musculature of the stomach and intestines. Animals in such a state have been observed repeatedly with the X-rays, and throughout a whole day the food has been seen lying in the stomach without the slightest sign of a peristaltic wave affecting it; or food that had entered the intestine was seen to be similarly unaffected by any motions of the gut. The animals manifest no signs of appetite and they do not eat spontaneously. From what we know of the vagus influence on the muscles of the canal, we may assume that the indolence or total inactivity of the muscular wall is due to lack of the tone necessary for peristalsis. In this connection it is of interest to know that when the stomach has been wholly disconnected from the spinal cord and brain and has acquired its own inherent or intrinsic tonic state, independent of any outside influence, peristalsis is not affected by the general debility of the organism as a whole.

The observations made on lower animals are easily duplicated in man. Alvarez speaks of autopsies on people who have died from botulism, in whose stomachs has been found food which had been eaten many days before, when the trouble commenced. Similar stagnation is often noticed in the stomachs of men and women suffering from tuberculosis and other infectious diseases. It is a tribute to his sure vision that Beaumont noted a similar phenomenon in his studies on St. Martin. Occasionally he observed a pathological appearance of the stomach associated with symptoms of general bodily disorder such as dryness of the mouth, thirst, exaggerated pulse, etc. Under these circumstances, he states, "no gastric juice can be extracted, not even on the application of alimentary stimulus . . . food taken in this condition of the stomach remains undigested for 24 or 48 hours, or more, increasing the derangement of the whole alimentary canal, and aggravating the general symptoms of the disease." Thus on one occasion (experiment 10 of the third series), when St. Martin "complained of headache, lassitude, dull pains in the left side, and across the breast—tongue furred, with a thin, yellowish coat, and inclined to dryness—eyes heavy, and countenance sallow," Beaumont reports the stomach still full of food six hours after a small breakfast of fried sausage, dry toast and a pot of coffee. About three hours later Beaumont suspended a roasted oyster in the stomach and his patient ate twelve more of them. After two hours he found, on withdrawing the suspended oyster, that it was not half digested. It is evident that the symptoms of general indisposition were associated with a marked disturbance of the processes of the stomach.

Not only debilitating disease but also exhausting labor is associated with failure of proper action of the digestive organs. In a man with a fistula Mantelli noted that for an hour or two after strenuous muscular exertion the stomach did not respond normally to the actual presence of food.

In addition to the effect of the vagi on the musculature of the alimentary canal, there is the effect of these nerves, and of associated nerves (which govern the salivary glands), on the digestive secretions. Many years ago Pavlov reported that in addition to the well-known psychic secretion of saliva there is also a psychic secretion of the gastric juice—a secretion due to the pleasant taste of food, that is, to the satisfaction of appetite. Later it was found that there is a similar secretion of the pancreatic juice. The psychic secretion from the stomach and pancreas is dependent upon the vagus nerve supply. This immediate psychic secretion is serviceable, of course, in starting off the digestive process in a satisfactory manner. In 1911 I suggested that attendant on the psychic secretion from the digestive glands there might be in the gastro-intestinal tract, when food is relished in anticipation or at the time it is eaten, a psychic increase of muscular tone, both being consequences of vagal excitation. This suggestion was associated at the time with the evidence that severance of the vagi *before* introduction of food into the stomach was not followed by gastric peristalsis; whereas, if the vagi were severed shortly *after* food was taken, the digestion at that particular meal was not seriously interfered with. It seemed, therefore, that the pleasurable eating of food was associated with some influence of the vagi on the gastric muscle similar to the influence of the vagi on the gastric secretion when food is ingested.

The foregoing evidence for psychic tonus has been supported by Alvarez. He had a patient with a large ventral hernia; such that the bowel was so thinly covered by peritoneum and skin that its contractions could be easily seen. When a nurse brought food, a peristaltic wave rushed down the bowel and was followed by active kneading movements. Hertz and also Lüdin have noted that a barium meal will pass along the gut faster if it is followed by a second meal given a short time after the first. The second meal would serve under these circumstances to increase the tone at the upper end of the intestinal tube. Observers have stated, furthermore, that contrast meals leave the stomach more rapidly if they are made palatable; and Alvarez again has noted in a patient with a jejunal fistula that the contractions of the bowels were more active when the patient ate by himself than when he was plainly annoyed by being fed by the nurse. Another patient, described by Alvarez, had an incompetent anal sphincter; he had to be extremely careful about eating, seeing, smelling, or even thinking about the pleasures of food, because of the stimulating psychic effects on peristalsis, and therefore on the tone of the intestinal musculature.

All these observations point clearly to the important relationships between the proper functioning of the gastro-intestinal tract and the general state of the organism. If the tract functions satisfactorily the energy-yielding food which is taken in by mouth and chewed and swallowed, becomes a means of supporting all of the activities of the organism in a highly efficient manner. If there is any interference with the digestive processes this influx of energy for bodily functions is interfered with and the whole organism suffers in consequence. On the other hand, if there is a debilitated or asthenic state as a consequence of exhaustion, whether from over-work or prolonged disease or acute infection, so that that moderate degree of activity which we have called tone is greatly reduced, the tonic state of the gastro-intestinal tract shares the tonelessness of the rest of the body; and as a result the organism is not able to carry on vigorously the processes of digestion. It is clear that under these circumstances a vicious circle may be established so that the debilitated organism does not receive the nutriment which is necessary for its upbuilding. In the past the careful physician has broken into this vicious circle by giving food which is easily digested and therefore requires minimal functioning of the digestive organs. At present, certainly in cases of inanition or malnutrition, it is possible to break into the vicious circle by means of insulin, which, by stimulating vagal tone and helping towards a better utilization of the absorbed food, definitely favors the restoration of the normal state.

At the beginning of this lecture I had occasion to outline the organization of the autonomic nervous system. Throughout the lecture I have referred repeatedly to the rôle of the vagal and sacral nerves as representatives of the parasympathetic divisions of that system. We may summarize the functions of the sacral division as a whole by the statement that they consist of a group of reflexes for emptying hollow organs which are periodically filled. Notable among these are the rectum and distal colon, and also the urinary bladder. The effective stimulus for contraction of both these viscera is the stretching of the tonically contracted viscus by accumulating contents. The functions of the cranial division likewise can be summarized as mainly a group of reflexes, but reflexes which are protective, conservative and upbuilding in their service. Thus the autonomic fibers of the third nerve narrow the pupil and protect the retina from excessive light. Other representatives of the cranial autonomic, associated with the seventh and ninth cranial nerves, provide for the flow of saliva. The tenth nerves (the vagi), as we have seen, carry the impulses for psychic secretion of the gastric and pancreatic juices and for establishment of the tonic state necessary for the periodic contractions of the alimentary tract. These nerves of the cranial division illustrate strikingly its upbuilding function, for they assure the essential basis for the proper digestion and for the absorption of the energy-yielding material which is required for all bodily activity.

These two divisions, the sacral and cranial, are similar in being largely subject to interference by striated muscle. Contraction of the bladder and rectum can be aided or frustrated by impulses from the cerebral cortex much as reactions of the iris can be induced or modified by voluntary acts. Indeed, as a rule, the workings of the cranial and sacral divisions on the digestive tract involve the coöperation of the cerebrospinal nervous system to a much greater degree than do the workings of the sympathetic division, because the cranial and the sacral are much concerned with orifices surrounded by striated muscles, at both ends of the tract. Thus food may be voluntarily swallowed in excessive amounts, so that the stomach is grossly distended; and when waste from the food is ready to be discarded, it may be voluntarily retained. It is because of this control of orificial functions by the cortex that the natural activities of the neighboring smooth muscle, under autonomic control, are not infrequently disturbed or subjected to unfavorable conditions. At our next meeting we shall see that the sympathetic division likewise may profoundly influence the functioning of the alimentary tract, not, however, because of cortical influence but because of emotional effects originating in sub-cortical regions.

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Chapter III

Digestive Disturbances Produced by Pain and Emotional Excitement

In the last lecture I tried to make clear the manner in which the digestive process might become inefficient, because in general bodily atony and debility the cranial division of the autonomic system is involved and fails, therefore, to perform its function of establishing tone in the musculature of the alimentary tract. And I mentioned also a probable corresponding inefficiency in calling forth the digestive secretions. In this lecture I wish to point out another way in which the digestive process may be profoundly disturbed through the positive action of the sympathetic division of the autonomic system, a division which, as we have already seen, is commonly opposed in action to the cranial division and which has, therefore, an inhibitory effect on muscular tone and on the secretions of the digestive glands. I would remind you that the sympathetic division is brought into action by a variety of conditions, prominent among which are pain and great emotional excitement.

The fact that emotional states can upset digestion has long been recognized. Beaumont reported the influence of extreme anger upon gastric digestion as observed in Alexis St. Martin. Violent passion, he declared, is likely to cause a reflux of bile into the stomach, a change in properties of the chyme, and a retardation or other disturbance of the chyme in its passage onward into the intestine. Similar observations have been made by more recent investigators who have had occasion to study gastric digestion in children whose esophagus has been closed because of inflammation and who, therefore, have had to be fed through a gastric fistula. For example, Hornborg found that when the boy whom he studied chewed agreeable food, there followed a typical psychic secretion of gastric juice. If the boy, however, became vexed and began to cry, the chewing of food was not accompanied by gastric secretion. This observation was confirmed by Bogen, who reported that when the child whom he examined fell into a passion, the giving of food after the child was calmed was for some time not followed by any flow of the juice. These observations on the effects of emotional excitement on gastric secretion are paralleled by corresponding observations on the movements of the stomach. Dr. Joslin has told me of a case that came to his attention. A refined and sensitive woman, who had had digestive difficulties, came with her husband to Boston to be examined. The next morning the woman appeared at the consultant's office an hour after having eaten a test meal. Examination of the gastric contents revealed the presence of a considerable amount of the supper of the previous evening. The explanation of this stagnation of the food in the stomach came from the family doctor, who reported that the husband had made the visit to the city an occasion for becoming uncontrollably intoxicated, and that by his escapades he had given his wife a night of turbulent anxiety. The second morning, after the woman had had a good rest, the gastric contents were again examined and the test breakfast was found to have been normally discharged. Hertz has reported the case of a man of most regular habits who was in a bad railway accident in which he was buried by the wreck of the cars for more than half an hour. He was so deeply affected by the experience that for days his bowels refused to act, although he used all sorts of agents to make them do so. Dr. Alvarez has cited the instance of a young woman, with digestive processes profoundly disordered, whose condition was brought back to normal only after he had paid the tax collector whom the patient, because of her negligence, had occasion to fear. These instances are common enough in the experience of any gastro-enterologist, and probably also in the experience of most general practitioners of medicine. Indeed, the statement has been made that fully 80 per cent of persons who consult physicians because of digestive disorders do so because of some disturbing emotional factor.

Not only emotion but also pain can affect the digestive process. Netschaiev, working in Pavlov's laboratory, showed many years ago that excitation of the sensory fibers in the sciatic nerve for two or three minutes resulted in a checking of the secretion of gastric juice that lasted for several hours. Similarly, in the motor aspects of digestive function, there may be a marked inhibitory effect produced by strong afferent stimulation. One of the most distressing instances of inactivity of the bowel is that seen occasionally after surgical operations on the abdomen. In 1906 Dr. F. T. Murphy and I undertook an analysis of the factors which are concerned in this post-operative inactivity. We found that it might be caused by handling the stomach and intestines; that is, it might be caused by local effects in the wall of the digestive tract, or trauma which might act reflexly. Such trauma during the standard half hour of etherization (which in itself, I may say, had relatively little influence on the discharge of food from the stomach and its passage through the intestines) in fact retarded the exit from the stomach for four or five hours and thereafter caused the discharge to be characteristically slow. The movement through the small intestine was likewise very sluggish. In only one case out of ten did the food reach the colon within six hours, whereas normally it would begin to appear there in about three hours. Of course the trauma in these experiments was performed under anesthesia, when nervous conduction involving reflex pathways is much depressed. No doubt painful experience in the absence of anesthesia would have effects which would be even more pronounced. Indeed, the expression "sickening pain" is testimony to the power of strong sensory stimulation to upset the digestive processes profoundly. Vomiting is as likely to follow violent pain as it is to follow strong emotion.

In the experiments performed by Murphy and myself we found that after severance of the splanchnic fibers of the sympathetic system the standard trauma resulted in no effect whatever. Indeed, the results observed in such cases compared favorably with those from animals in quite natural conditions. After splanchnic section, likewise, the effects of emotional excitement are no longer noteworthy. There may be some inhibitory action produced by way of the vagus nerves, but vagal impulses are not nearly so efficient in stopping gastric peristalsis or the segmenting movements of the small intestine as are the impulses delivered from sympathetic sources.

Many years ago, when I first noticed that emotional excitement caused inhibition of the movements of the stomach and intestines and learned also that it depressed for a considerable period the action of the digestive glands, it seemed to me that the rational procedure would be to interrupt the sympathetic channels through which these inhibitory effects are produced, in order that so beneficent and so fundamentally important a process as that of digestion should not be interfered with. At that time I did not thoroughly comprehend the organization of the sympathetic system for diffuse distribution of its influence and did not realize how widespread were the effects of its activities. Only gradually, as new evidence came in, did I learn that in addition to the well-known acceleration of the heart and rise of blood pressure that result from emotional disturbance there is a complex of other changes, including redistribution of blood in the body, a discharge of extra corpuscles from the spleen, a more rapid coagulation of the blood, an increase of blood sugar, and a dilation of the bronchioles. If we consider this complex of changes associated with pain and great emotional stress, we perceive that the inhibition of the digestive process is but a single item in the total variegated picture. Only by understanding the significance of the total change can we interpret the disturbance of digestion. I propose, therefore, that we consider now the ways in which the sympathetic system can affect the body.

The best mode of obtaining an insight into the functions of the sympathetic system is by learning the conditions which bring it into action. Prominent among such conditions are external cold, hypoglycemia, motion and emotion.

We are all familiar with one effect of external cold, as seen in domestic mammals and birds. The roughened hair of the horse or the cat and the ruffled feathers of the fowl on a cold morning are indicative of sympathetic action, because the smooth muscle which erects the hairs and feathers is under sympathetic control. Human beings, as highly evolved mammals, have degenerate skin appendages and therefore "goose flesh" is the only obvious manifestation of this effect of cold. If you examine closely the little hummocks of goose flesh you will find standing upright in each one a minute hair. The question arose as to whether this activity of the sympathetic system in response to external cold was associated with discharge of the adrenin from the adrenal medulla. If so, it would be a matter of some importance because adrenin is capable of accelerating the processes of combustion in the body, much as putting a blower on the fire accelerates the burning of the coal. Thus extra heat would be produced in the organism at a time when it would be especially useful. In order to test this possibility we made use of the denervated heart, *i.e.*, severing all connections of the heart with the central nervous system, but leaving the recurrent laryngeal branch of the right vagus to innervate the larynx and the left vagal trunk to care for digestion. The operation, which was of course done with surgical precautions, involved also removal of the upper thoracic sympathetic chains. Animals thus operated upon lived indefinitely in the laboratory in good physical condition. The denervated heart is extraordinarily sensitive to increase of adrenin in the circulation. It beats faster when there is an increase of adrenin by one part in 1,400,000,000 parts of blood. The beat of the heart can be registered simply by holding a receiving tambour against the chest wall and letting the cardiac impulse, as transmitted through a tube to a recording tambour, write its tracing on a smoked surface.

If an animal thus prepared, and quite recovered from the operation, is placed comfortably on a cushion near a window during cold weather the raising of the window results, within a few moments, in a typical erection of the hairs in response to the cold. Associated with this evidence of sympathetic activity there is an increase in the rate of the denervated heart. The increase may amount to 30 or more beats per minute. If the adrenal glands are now inactivated, *i.e.*, if one is removed and the nerves to the other are severed, so that adrenal secretion can no longer be excited, exposure of the animal to cold in the same manner as before results in no noteworthy increase in the heart rate. Indeed, the rate may actually fall. It is clear, therefore, that the sympathico-adrenal system is stimulated to activity in cool surroundings when the temperature of the body is likely to fall. The erection of hairs serves to enmesh about the body a layer of air which is a poor conductor of heat. Associated with this is a constriction of the surface blood vessels so that the warm blood from the interior of the body is less exposed to the surface, where it would lose heat. By these two procedures heat loss is minimized. The extra discharge of adrenin accelerates the burning process, and thus the temperature of the body is further prevented from falling. If the adrenal glands are inactivated and animals are then subjected to a standard degree of cold, the organism falls back upon shivering as another means of providing the needed extra heat. It is obvious from these considerations that a primary function of the sympathetic is the protection of the body against a lowering of body temperature.

You are all familiar with the fact that if insulin is given in excess there is produced a characteristic state known as the "hypoglycemic reaction," attended by sweating, a faster pulse, and dilation of the pupils. These phenomena are all indicative of activity of the sympathetic system. Again the question arose as to whether the adrenal glands were involved. If so, it was a matter of some importance to determine the fact, because adrenin is effective in liberating sugar from storage from the liver. Thus a condition of hypoglycemia would be rectified by physiological action in a natural manner through discharge of sugar from the hepatic reservoir. Again, it was possible to make use of the denervated heart.

If insulin was given when the adrenal glands were out of action the blood sugar fell continuously, with no increase in the rate of the denervated heart, even though the glycemic percentage was reduced to the convulsive level. It is noteworthy that the drop in the blood-sugar concentration was almost in a straight line, *i.e.,* at almost a uniform rate. When, however, insulin was given with the adrenal glands in place and ready to act, the blood sugar fell only to a certain point—a critical point—whereupon the denervated heart began to beat more rapidly and continued to accelerate as the fall continued further. The acceleration of the denervated heart was, of course, due to discharged adrenin, because it failed to occur when only one factor was lacking, *i.e,* the adrenal glands. As soon as this indication of adrenal discharge appeared it was interesting to observe a check in the fall of blood sugar. This pointed clearly to a liberation of extra sugar from reserves in the liver, for adrenin is known to have that effect. It seemed clear, therefore, that a protective arrangement was at work shielding the organism from the dangers of excessive hypoglycemia.

Good evidence that this protective service was being performed by the sympathico-adrenal system was obtained by selecting a dose of insulin which, in normal animals, barely failed to cause a reduction of blood sugar to the convulsive level. The action of this barely subconvulsive dose was then studied in animals which were deprived of the service of the sympathico-adrenal apparatus by extirpation of one adrenal gland and denervation of the other. The typical effect of this standard dose under these circumstances was to produce convulsive attacks within a relatively short period of time. Further confirmation of this evidence was reported by Macleod and collaborators, who noted that if rabbits had been well fed, so that the liver stores were satisfactorily stocked, a given dose of insulin would cause a fall of blood sugar to a relatively low level, whereupon the glycemic percentage would begin to rise and would be restored to normal. Here is an example of the efficient corrective action of the sympathico-adrenal system. It is obvious that that system acts to protect the body from a disastrously low percentage of blood sugar when conditions are such as to tend to lower it.

I mentioned earlier that both motion and emotion will bring the sympathico-adrenal system into play. The evidence that strong emotion will have that effect is known to everybody. The cat frightened by the dog has hairs standing erect all along its body, from the top of the head to the tip of the tail. The pupils are dilated, the pulse is rapid, and there are internal changes, such as increase of blood sugar and increase of red blood corpuscles (from contraction of the spleen), all of which indicate that the excitement has caused a discharge of sympathetic impulses. The question again arose as to whether there is a discharge from the adrenal medulla under these circumstances. For many years this question was in controversy. Stewart and Rogoff of Cleveland declared that the discharge of adrenin was steady and uniform, and they refused to accept the evidence that had been adduced to show that adrenal secretion is increased in the blood as a consequence of emotional stress. The denervated heart allowed definite evidence to be obtained on that point, for the animal with heart denervated could be observed any number of times under circumstances experimentally produced before inactivating the adrenals, and could be observed any number of times thereafter under the same circumstances, and the difference in the response of the heart clearly and permanently registered.

When the experiment just described was performed, it was found that not only did strong excitement cause an acceleration of the denervated heart but even minor activity, such as rising from a cushion and walking across the floor, would have that effect. To be sure, slight exercise had only little influence. In one experiment, for example, walking caused an increase of the heart rate by approximately 20 beats a minute. Later, when the animal (a cat) was resting on a cushion and a dog was brought near, and the hairs were erected and the cat hissed in a simple emotional response, there was a larger increase—approximately 40 beats a minute. When now the animal was placed in a cage and the dog was allowed to bark and make aggressive movements so that the cat responded vigorously, the heart rate, as soon as the animal could be removed from the cage and its cardiac impulse registered, manifested an increase of over 70 beats a minute. When this same animal was put through the same series of conditions after inactivation of the adrenal glands, minor exercise caused no increase in the heart rate, simple emotional excitement caused an increase of only 2 beats a minute, and excitement with struggle an increase of approximately 8 beats instead of 72. This increase of 8 beats belongs to another story, for it was the occasion of the discovery of a substance given off from smooth muscle when stimulated through sympathetic channels—a substance which we have given the name "sympathin." From these observations it is clear that both motion and emotion are accompanied by a discharge of adrenin from the adrenal glands and that therefore in these circumstances the sympathico-adrenal system is at work.

That the sympathico-adrenal system is excited to action in profound emotional disturbances, such as fear and rage, and that associated therewith the heart beat is accelerated, the blood pressure is raised, the circulating red blood corpuscles are increased in number, and the blood in the body is redistributed so that it is sent away from the splanchnic area and driven in greater volume through the brain and the muscles; and furthermore, that there is a discharge of sugar from the liver, a hastening of the process of coagulation of the blood, a dilation of the bronchioles, and a pouring-out of sweat—that all these phenomena occur as a consequence of excitement led to the suggestion of the emergency theory of sympathico-adrenal activity. That theory was based on the view that the powerful emotions, fear and rage, are linked with instinctive behavior which may involve maximal muscular effort. Thus the emotion of rage is associated with the instinct to attack, and the emotion of fear is associated with the instinct to run or escape. When under natural conditions enemies confront each other, these two emotions may be supremely aroused and the instincts may develop into a supreme struggle for existence. In this balance between triumph and disaster lies the key for explanation of the bodily changes which accompany great excitement. All the vascular adjustments—the rapid heart, the increased blood pressure (with larger volume of flow through brain and muscles), the increased number of red corpuscles—are useful in supplying a larger delivery of oxygen where supreme activity is likely to be going on, *i.e.,* in the neuromuscular apparatus. The dilation of the bronchioles adjusts the respiratory system to the greater need of an adequate oxygen supply and a larger riddance of carbon dioxide. The sugar freed from storage in the liver gives to the laboring muscles the source of energy which they need for continued action. If in struggle there is damage to blood vessels, faster clotting of the blood helps to check the loss from the body of this most precious fluid.

The foregoing considerations again point to the sympathico-adrenal system as a protective agency in times of crisis. Associated with the redistribution of blood in the body, a redistribution which involves sending the blood away from the splanchnic area to the active muscles and their nervous governors, there is necessarily a relative anemia of the gastro-intestinal tract. It is under these circumstances that the gastro-intestinal functions are inhibited. We see, therefore, that the disturbances of digestion, which we have been considering, are part of a larger complex of reactions in the organism, which, in the development of higher animal forms, have played an important rôle in the conflicts which have determined survival. At a critical juncture it is appropriate that the digestive process, beneficent though it is, shall be set aside temporarily in order that the organism as a whole, by functional readjustments, may have a more favorable chance in meeting the decisive demands of the moment. As I view the conditions which prevail in civilized society, I regard the emotional disturbance of digestion as being induced after the traditional dangers in the long history of our race have largely disappeared. It is rare, indeed, that we are emotionally excited by circumstances which demand supreme muscular effort. We become excited, for example, by watching a game, or by facing an examination, or by learning bad news, *i.e.,* when no struggle is called for. The digestive processes, however, may be quite as much upset by these incidents as if the utmost physical exertion was anticipated. Only by understanding these larger aspects of the response to excitement can we explain to patients what an emotional derangement of digestion means, and how foolish it is to allow the organism to get into fighting trim, with possibly disastrous stoppage of the digestive process, when no fighting is required.

The views which I have just developed have received a more extensive application through recent studies, which have been made on animals from which the sympathetic system has been wholly removed. You will recall that the outlying neurones of this system are arranged in two chains, reaching from the superior cervical ganglion to the pelvis, on either side of the spinal column. Long ago Langley and Anderson showed that if the outlying neurones are removed the preganglionic fibers, growing out from the spinal cord, can not make effective junction with the smooth muscle and glands that are normally innervated by the postganglionic fibers. Removal of the sympathetic chains, therefore, definitely eliminates the sympathetic control of the glandular organs and those managed by smooth muscle.

In our first operations we removed the sympathetic chains in parts,—the cervical, the abdominal and the thoracic. The fault of this method lay in the possibility of overlooking some ganglia in the lower thoracic region behind the attachment of the diaphragm. In our later operations we removed each of the chains intact, an unbroken string of ganglia, from the stellate at the top of the thorax to fused masses in the pelvis. Removal of the stellate ganglion renders unnecessary the extirpation of the cervical ganglia, because the preganglionic fibers of these ganglia pass through the stellate and are therefore interrupted when that ganglion is removed.

The first and most striking fact that appears in an experience with these sympathectomized animals—which, as you recognize, are really new types of organisms in the world—is that they live in the conditions of the laboratory quite normal lives without any serious difficulty. Two such animals were kept in the laboratory for more than three years before they were used for post-mortem examination. They digest their food normally, they gain in weight, they grow to adulthood in a natural manner if the sympathetic is removed when the animal is young, and they have an essentially normal metabolism. Females take their part in the process of reproduction. Males, however, are sterile, because seminal ejaculation is stopped.

The question has been raised as to possible innervation of skeletal muscle by the sympathetic system. Some years ago Hunter and Royle made the assumption that the spastic contraction of skeletal muscle, occurring after cerebral injury, was due to an excessive discharge of sympathetic impulses delivered to the muscle. This view they supported by experiments in which, so they stated, the rigidity of the limbs after removal of the cerebral cortex was present on the normal side but absent on the sympathectomized side. For orthopedic purposes, therefore, they advocated the operation of cutting the rami which carried the sympathetic fibers distributed to the spastic limbs. According to their accounts, there resulted a lessening of the spasticity and a remarkable improvement in the control of the limbs. Later work by many observers has failed to support the experimental observations of Hunter and Royle. Work done at the Harvard Laboratory by Forbes and others revealed no influence of the sympathetic system on the rigidity that follows decerebration. There was, to be sure, a variation of the rigidity on the two sides of the body dependent upon the position of the head. It seems possible that Hunter and Royle, in their original observations, failed to take this matter into consideration. It is significant that after total removal of the sympathetic system no variation in muscular tone is observable. When one of our animals, from which one abdominal sympathetic chain had been removed for some time, was presented to Dr. Royle for test of its knee jerks, he was unable to distinguish any difference on the two sides which would permit him to judge which side was sympathectomized. The bulk of evidence is opposed to the idea that there is a sympathetic control of tone in skeletal muscle.

If life, growth, metabolism and muscular action are unaffected by sympathectomy, what importance has the sympathico-adrenal system? We can understand better the functions of that system if we spend a few moments considering our two environments. As Claude Bernard pointed out many years ago, we not only have the external environment with which all of us are acquainted—the environment consisting of the agencies in the outer world which affect our sense organs and which we use for our purposes—but also a less well-known internal environment composed of the fluids of the body. All of our living parts, all of the varieties of cells which compose our active organs, are bathed in these fluids—the blood and the lymph. These fluids are the product of the organism itself and are under the control of the organism. It is in the highest degree important that they be kept relatively constant. You are familiar with the fact that if the percentage of blood sugar rises from 100 to above 170 mg. per cent, it escapes from the body through the kidneys. On the other hand, if it falls as low as 45 mg. per cent, convulsions are likely to occur; and a further fall may be associated with coma and death. Again, if the calcium content of the blood, which is normally 10 mg. per cent, rises to 20 mg., the blood becomes so viscous that it will hardly circulate, whereas if it falls from 10 to about 5 mg. per cent convulsions supervene. Similar need for constancy is seen in the relation of acid and base in the blood. If the pH, which is normally about 7.4, falls to 6.95—a very slight change—coma appears; and if it rises from 7.4 to 7.7 there are convulsive attacks. Analogous limits of temperature variation are imposed on warm-blooded animals. The body temperature cannot remain long at 108° or 109° F. without causing irreversible changes in delicate nerve structures of the brain; and although the temperature may fall from approximately 98° to 75° F. without causing death, that low temperature is incompatible with bodily activity. These extreme variations which I have mentioned are ordinarily not permitted. When shifts occur in either direction above or below the normal they are, of course, to some degree shifts in the direction of excess, but long before the excess is reached devices are set at work which prevent the extreme stage from being reached. I have already illustrated the protective arrangements provided in the sympathico-adrenal system, when there is constriction of surface vessels and discharge of adrenin if the temperature tends to fall, when there is liberation of sugar from the liver if the blood-sugar level is reduced beyond a critical point, and when the circulation is accelerated so that extra oxygen is delivered and excess of carbon dioxide is carried off if muscular exertion is vigorous. It is clear that the sympathico-adrenal system offers an automatic stabilizing device for maintaining uniformity of the internal environment. And just insofar as this internal environment, or fluid matrix, in which our living parts reside is kept uniform, we are freed from the limiting effects of both external and internal changes.

Further evidence of the importance of the sympathico-adrenal system in maintaining constancy of the internal environment is found in the characteristic behavior of sympathectomized animals when they are subjected to conditions of stress. If, for example, they are exposed to cold the hairs are not erected. Also the peripheral blood vessels are not constricted, and therefore the body heat is poorly conserved. The secretion of adrenin, which, as we have learned, is useful in accelerating the metabolic rate so that there is increased production of heat, does not occur. For these reasons you would expect that exposure of these animals to cold would reveal their deficiencies. As a matter of fact, it does so. When such animals are placed in a cold room the body temperature promptly begins to fall. Exposure of normal animals to the same low temperature has no such effect. The body temperature of sympathectomized animals drops perhaps 4° or 6° F., and then by shivering they are usually capable of preventing a further drop to a lower level. This deficiency in temperature regulation does not ordinarly manifest itself because the animals live in the warm rooms of the laboratory during the winter months and are therefore not subjected to exacting conditions. It is noteworthy, however, that when they can do so they resort to radiators and other sources of warmth much more frequently than do normal animals.

Not only are the sympathectomized animals sensitive to cold; they are also sensitive to heat. In order to prove whether an animal that takes the upright position could withstand removal of the sympathetic system, the operation was performed on a monkey. When on a warm June morning this animal was placed with some other monkeys in the yard in order that they might enjoy fresh air and sunlight, it was soon found that the animal that had been operated upon was in collapse, with a high temperature. Indeed, the animal died of heat stroke. We depend on the sympathetic system not only to protect us against heat loss but also against high temperature.

When sympathectomized animals are emotionally excited there is no rise of blood sugar, instead of the usual rise of over 30 per cent. The blood pressure instead of being elevated is actually depressed by excitement and struggle, and the emotional polycythemia which occurs in consequence of contraction of the spleen is wholly lacking. It is clear that these changes, which, as we have learned, may be regarded as preparations for action, would not occur when action itself took place. There would be no redistribution of blood in the body, a fall of blood pressure instead of a rise, only a slightly increased heart rate (resulting from diminished vagal tone), and no blood sugar for continued activity. Under such circumstances we should expect a very considerable reduction in the capacity of the animal to work. Actual observations on a dog trained to run in a tread mill until exhausted proved that sympathectomy greatly reduced the capacity of the animal to perform.

The facts which we have just reviewed bring out emphatically the functioning of the sympathetic division in maintaining constancy of the internal environment. If this internal environment were not kept constant in cold weather, for example, we, like lower animals such as the frog, or like mammals which have not adequate control of their body temperature, should have to become inactive in hibernation. We are rendered independent of such external changes of temperature by the functioning of the sympathetic division as a protector of the constancy of the fluid matrix. This division likewise renders us independent of possible disturbances which might be caused by our own actions. In muscular struggle, for example, sugar is used up, and were it not for the service of the sympathetic in liberating extra sugar from storage we should soon suffer from hypoglycemia in consequence of muscular effort. Furthermore, when we engage in vigorous physical struggle heat is produced in excess. Indeed, so much heat results from maximal muscular contraction that at the end of three miles of a boat race the oarsmen, if they could not be rid of the heat, would be stiff in coagulation—you will please pardon the incongruity! Of course, this condition is not even approached, because, through operation of the sympathetic system, the surface blood vessels dilate, and sweat is poured out, and thus the extra heat is dissipated. Again, vigorous physical struggle develops a large quantity of lactic acid. The amount thus produced would easily overwhelm the alkaline buffer in the blood if that were the only protection against the development of an acid reaction. The dangers which might result from the shift to an acid reaction are obviated, as we have seen, by acceleration of the heart, contraction of the splanchnic blood vessels and discharge of stored corpuscles from the spleen, all of which changes are managed by the sympathetic system, and all of which are directed towards delivery of additional oxygen to the active organs, the burning there of the non-volatile lactic acid to volatile carbon dioxide and water, and the carriage of the carbon dioxide to the lungs for discharge from the body.

Associated with violent effort and simultaneous coöperation of the sympathico-adrenal system there is, as we now can readily understand, a disturbance of the digestive organs. As Beaumont noted, "severe and fatiguing exercise retards digestion." He offers two reasons for this effect: "the debility which follows hard labor of which the stomach partakes; and the depressed temperature of the system, consequent upon perspiration, and evaporation from the surface." In the light of our present understanding we should attribute the "debility which follows hard labor" to a lack of tone in the digestive organs because of the participation of vagus functions in the general bodily exhaustion. Although we should not lay so much stress on the "depressed temperature of the system" because of perspiration and the evaporation of sweat from the skin, we should today recognize that it is the diffuse influence of the sympathetic system, causing not only the outpouring of sweat but also the inhibition of gastric and intestinal activities, that would account for digestive derangement in severe exercise.

We are now in a position to understand fully why removal of sympathetic influences, in order to avoid a disturbance of digestion, would be an irrational procedure. Since this system has as its primary function the maintaining of constancy of the fluid matrix, any change lessening its influence would equally diminish its effectiveness in carrying on that essential function.

We are also in a position now to understand more fully how persistent emotions may interfere with the beneficent services of the gastro-intestinal tract to the organism. As we have already seen, the changes accompanying emotional excitement are similar to those which occur in times of vigorous effort. They have been interpreted, therefore, as preparations for such effort.

If the emotion is transformed into action, then the preparation is useful, and the body by anticipation is protected against a low blood sugar, an excessive heat, and a limiting shift in the direction of acidity of the blood. If no action succeeds the excitement, however, and the emotional stress—even worry or anxiety—persists, then the bodily changes due to the stress are not a preparatory safeguard against disturbance of the fluid matrix but may be in themselves profoundly upsetting to the organism as a whole. Woodyatt has described a man with diabetes who was being carefully observed under rigorous conditions in a hospital and who had no glycosuria. Suddenly one day, without alteration of his regimen, there was a large discharge of sugar in the urine. Inquiry revealed that he had just learned from the firm which he had served for many years that he had been discharged. The worry and anxiety under these circumstances were the occasion for a marked exacerbation of his pathology. Cabot has cited the case of a man in a hospital with a broken leg. His nutrition was strangely and inexplicably defective and the leg was slow in healing. At last it was learned that he had been worrying about the condition of his family. When he was reassured regarding their state, his digestive and assimilative processes were soon restored to normal and the healing rapidly progressed.

Like other involuntary functions it is possible to condition emotional reactions. You are probably familiar with the experiments of Pavlov, who showed that when two stimuli—one of them a natural stimulus such as acid or food in the mouth for the flow of saliva, and the other an indifferent stimulus such as the ringing of a bell—act simultaneously, there will occur, after the coincidence has been many times repeated, a flow of saliva in consequence of the ringing of the bell, *i.e.,* when the indifferent stimulus alone is acting. There may be a similar relationship developed between significant and indifferent factors in disturbances caused by emotional experience. The circumstances which attended the original occasion for the emotional upset may cause a recurrence of the upset. I well recall in my own experience an incident of digestive distress which was associated with eating food seasoned with mayonnaise dressing. For weeks thereafter the sight or odor of that sort of dressing brought back in a very disagreeable form the original experience, although the dressing as such had nothing to do with the original disturbance. Doubtless many of you will recall similar instances to which you could refer.

What do these considerations of the influence of emotions on digestion suggest in the way of practical advice? It seems to me that inasmuch as we now understand that the total complex of bodily changes associated with emotional excitement are properly interpreted as preparation for struggle, we should attempt to take a rational attitude towards any exciting incident which may occur. We should decide that if there is action to be engaged in, the excitement should be allowed to run its full course without limitation. If there is nothing to be done in the circumstances, however, it is obviously unwise to permit the organism to be deeply disturbed and especially the fundamentally important functions of digestion to be inhibited. You may object that emotional excitement is not under voluntary control and that therefore we cannot check its course. I can testify from personal experience, however, that since I have come to understand the function of the strong emotions and have realized the widespread and profound perturbations which they may uselessly cause in the body, I have been able to take a rational attitude which has minimized the extent of their influence.

Another suggestion which may be offered is that when an occasion arises which provokes a degree of excitement that cannot be controlled, the reasonable behavior is that of working off in hard physical labor the bodily changes which have occurred in preparation for vigorous effort. Often the excited state can thus be reduced and the body, instead of being upset, is restored to normal.

In concluding this series of lectures I wish to tell you how deeply grateful I am that you gave me the privilege of celebrating with you the centenary of the culmination of Beaumont's studies. I have shared with you an admiration for the spirit in which he carried on his investigations, and I have rejoiced that I could take part with you in this memorial to his achievement.

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