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NOTES ON THE DIGESTION OF "LIVING" TISSUES.

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In a recent number of the *Biologisches Centralblatt*, Frenzel [1] has again called attention to this enigma of the digestive process, which, ever since John Hunter's day, has awakened much interesting and ingenious speculation, but which is hardly nearer a solution now than then. The question is: Why do organisms which manifest such power of digesting and assimilating the material they require, leave quite intact those organs or tissues where these processes go on so actively? Why does the stomach digest various albuminous substances so readily, and yet fail to attack its own walls, containing substantially the same material? Why do the intestines, with their much more varied power of digestive action, remain undisturbed and uninjured by this activity? Why does the pancreas secrete at least three vigorous digestive ferments, and yet work on unaffected by each and all of them? The same question may be urged concerning the various glands of many lower organisms which have a well-defined digestive tract; and the enigma only grows in difficulty and interest as we consider those forms of life where such a differentiation of organs does not appear to be present, and where processes at least analogous to the digestion of higher animals are carried on.

This immunity, in its completeness, is found only so long as the organism is alive. When death has occurred, a certain amount of post-mortal "self-digestion" is observable. The human stomach, for example, is not infrequently found with its walls so much softened and changed, that such a proteolytic action of its own secretions is supposed to have taken place.

[1] Verdauung lebenden Gewebes und Selbstverdauung. Von Dr. Johannes Frenzel. Biol. Centralblatt, VI., 681.

It has but rarely been observed that such changes are brought about before death. One of the few apparently authentic cases of ante-mortal self-digestion of the living human stomach was reported, a number of years ago, by Mayer;[2] and is given in detail, by Leube, in "Ziemssen's Cyclopædia."[3] It has been considered probable that, in ulcerations of the stomach, as well as in the course of cancerous changes of that organ, a certain amount of localized digestion of the gastric walls occurs, and this view has much in its favor.

Frenzel points out that a similar post-mortal transformation is observable in the entire animal kingdom. Certain sections of the intestines of insects are found thus self-digested; and the like change may be noticed in ferment-producing glands (the so-called "liver") of crustaceans and mollusks. He also considers that the rapid disintegration of many amœbæ and infusoria is due to self-digestion by the ferments they produce while living. Ordinarily these rapid changes are attributed to the activity of the bacteria of putrefaction; but Frenzel reports an observation which seems to lessen the necessity of such an assumption, or, at least, suggest caution in its universal application. He studied a worm which lives in strong vinegar (anguillula aceti), where, as he says, he could find no microbes. This worm, after death, showed a rapid dissolution of its tissues; and Frenzel thinks that the secretions of its digestive organs must have played an important part in the process. It should not be forgotten, in this connection, that, so far as I know, it has not been demonstrated that these post-mortal changes are true digestions, and not merely transformations into soluble bodies, without the formation of peptones. This distinction, as I think we shall see, is not unimportant.

The explanations that have been given concerning the protection which living tissues appear to possess have varied in an entertaining and instructive manner.

[2] Deutsches Archiv für klinische Medicin, 1871.
[3] Vol. VII, p. 261, of the American Edition.

It would take too much space to point out all the different phases through which the discussion has passed; nor would it be very profitable to examine all the theories proposed concerning the conditions which favor the post-mortal softening of the stomach itself. The literature may be found in sufficient fulness in Leube's article, already alluded to, and in Widerhofer's chapter on "Gastromalacia."[4] It will be enough for my present purpose to indicate the general principles which have been adopted, at various times, as the basis for an explanation.

It has been urged that the stomach preserves its integrity, first, on account of its life — by some "vitality"; or, on account of the protection afforded by its epithelium; or, again, because so much mucus is present as to enwrap the food, or cover the surface of the organ; or, finally, because the acid is neutralized by the alkaline blood, the exceeding vascularity of the stomach in active digestion rendering the acid harmless so soon as it reaches the tissues of the gastric wall. Each of these explanations, alone or in various combinations, has found its defenders; and yet no one of them, nor all of them together, can be considered satisfactory.

The supposititious protection afforded by the mucus[5] has the least claim upon our attention. This, if it worked by any alkalinity it possessed, could only hinder the proteolytic action by weakening the acid, whose presence is indispensable. If the protection be sought in the coating which is given to the stomach or to its contents, the explanation must at once appear to us to be unreasonable. How could any such coating be assumed to be permeable for acid and pepsine in one direction (that is, towards the mass to be digested), and to permit the passage of digested or dissolved material in the opposite direction (towards the

[4] Gerhardt. Handbuch d. Kinderkrankheiten, IV, 2, II, p. 425.

[5] Cf. Harley. "Contributions to our Knowledge of Digestion." British and Foreign Medico-Chirurgical Review, Vol. XXV, 1860 pp. 206-214.

gastric walls) and yet not allow the acid-pepsine mixture to pass with equal freedom.

Should we confine this explanation to the small intestine, with its alkaline digestion, as Claude Bernard seems to have done, a still further and more weighty objection may be found in the fact noted by Frenzel, that insects have no such layer of mucus in their intestinal tract, and yet no self-digestion occurs there during life.

The protection attributed to the epithelium, whether it be thought to lie in its own resistance to digestive changes, or in its rapid renewal, would appear also to be insufficient. It has been found that the epithelium may be quite extensively injured or removed,[6] and no digestion of the underlying tissue takes place. The reports of cases where sounds and stomach-pumps have produced lesions of the epithelium, appear to be confirmatory of the view that the protection of the stomach is not to be sought in this coating, or, at least, not alone therein.

The alkalinity of the blood and the lymph, as a possible defence against the attack of the gastric juices, would, at the first glance, appear to be much more acceptable. The localized self-digestion of ulcerations, or in cancer, might be attributed to altered blood-flow, and consequent lessening of alkalinity. In the marked case of gastromalacia given by Leube and Mayer, and already quoted above, the individual had extensive cicatricial contractions at the pylorus, as well as at the cardia; and these would probably materially alter the blood-supply.

In this connection, however, we may not pass over in silence an observation made, several years ago, by Edinger.[7] He injected a solution of alizarin into the bloodvessels, and inferred, from the color-changes,

[6] Pavy. Medical Times and Gazette, 1863, Vol. II, p. 286. This is an abstract of a paper read before the British Association. See, also, Harley, loc. cit.

[7] Edinger. Ueber die Reaction der lebendigen Magenschleimhaut Pflüger's Archiv f. d. ges. Physiologie XXIX, 247.

that the mucous membrane of the stomach has an acid reaction throughout a considerable portion of its substance when active digestion is going on. Unfortunately, his method is not delicate enough to permit a microscopical examination of the tissues.

Even if we accept fully the view that the alkalinity and vascularity of the gastric walls preserve them from digestive destruction, we advance but a little towards a solution of our larger problem. In the small intestines we find a no less active digestive process, and a much more varied one, which is carried on in an alkaline menstruum. If the alkaline blood protect the stomach, what is the power which guards the walls of the smaller intestines?

The oldest explanation is that commonly attributed to John Hunter. This finds the immunity of the digestive apparatus in its "life" — in its vitality. Modern biology cares so little for any "vital principle," that such a view seems almost absurd, since it merely answers one question by putting another — a method not quite out of fashion. Could we turn backward mentally, and think as did the strong men of old, as readily as we may masquerade in their clothes we should doubtless perceive that in this view John Hunter was fully abreast of his time. We might realize that we are not any too near an answer of our enigma nowadays, although we have turned the question completely round.

It is, perhaps, not without interest to read what Hunter wrote on this point. The original paper, "On the Stomach itself being Digested after Death," was presented to the Royal Society, and read June 18, 1772. It was printed in the sixty-second volume of the "Philosophical Transactions," and reprinted, with slight changes, as an appendix to "Some Observations on Digestion." The paragraphs which state the doctrine are as follows: [8]

[8] I quote from page 184 of the "Observations on Certain Parts of the Animal Œconomy," by John Hunter. London, 1786.

"An animal substance, when joined with the living principle, cannot undergo any change in its properties but as an animal; this principle always acting and preserving the substance possessed of it from dissolution, and from being changed according to the natural changes which other substances undergo.

"There are a great many powers in nature which the living principle does not enable the animal matter, with which it is combined, to resist, viz., the mechanical and most of the strongest chymical solvents. It renders it, however, capable of resisting the powers of fermentation, digestion (and perhaps several others), which are well known to act on this same matter, when deprived of the living principle, and entirely to decompose it." . . .

"Animals, or parts of animals, possessed of the living principle, when taken into the stomach, are not in the least affected by the powers of that viscus so long as the animal principle remains; hence it is that we find animals of various kinds living in the stomach, or even hatched and bred there: yet the moment that any of those lose the living principle, they become subject to the digestive powers of the stomach. If it were possible for a man's hand, for example, to be introduced into the stomach of a living animal, and kept there for some considerable time, it would be found that the dissolvent powers of the stomach could have no effect upon it; but if the same hand were separated from the body, and introduced into the same stomach, we should then find that the stomach could immediately act upon it.

"Indeed, if the first were not the case, the stomach itself ought to have been made of indigestible materials; for were not the living principle capable of preserving animal substances from being acted upon by the process of digestion, the stomach itself would be digested.

"We find, on the contrary, that the stomach, which at one instant, that is, while possessed of the living

principle, was capable of resisting the digestive powers which it contained, the next moment, viz., when deprived of the living principle, is itself capable of being digested, not only by the digestive powers of other stomachs, but even by the remains of that power which itself had of digesting other things."

A similar statement, but much more picturesquely put, may be found among his posthumous papers. I quote from page 146, Vol. I, in the edition prepared by Owen.[9]

"The [power of the] containing [organ] may, and does depend on the disposition of the body and mind, not so much on the constitution or strength of the body; for many weak constitutions have vast power of digestion, and others the reverse. Its effects are immediate on dead substances; almost as quick as the effects of an acid on an alkali. Its power depends upon life; for as soon as life is gone, even in the most healthy, this power is lost, excepting what may be going on [at the time of death], which continues for a little time. It depends on a living principle in itself; but that which is to be digested must be dead, or have lost this living principle, or it cannot be dissolved. . . . If it was possible for an animal to live in the stomach of another animal, supposing digestion not to be going on in that stomach, it would then live while digestion was going on; for that animal would not be in the least dissolved, because the living principle in the animal would prevent or counteract the digestive quality of the stomach. If this was not the case then we might readily suppose that even though the animal life was not immediately affected by the digestive power, yet at last it might be destroyed by the external and extreme parts of the animal being digested, and so the animal be obliged to die, like a person with a mortification. But that a living animal will not be so dissolved is every day proved by worms,

[9] Essays and Observations on Natural History, Anatomy, Physiology, etc. 2 vols. London, 1861.

maggots of flies, living in the stomachs of many animals; and if it was a power that could act upon a part that had the living principle, as well as an acid can, then the stomach itself would certainly be dissolved. If one could conceive a man to put his hand into the stomach of a lion, and hold it there without hindering the digestive powers, the hand would not in the least be digested; and if the hand of a dead man was put in at the same time, whether separated or not from the body, that hand would be digested while the other would not."

A rather different but no less entertaining view as to the importance of the vital principle in the digestive act, may be read in the note below, although the point before us is not directly involved.[10]

The following extracts from Saumarez' "New System of Physiology," published at London, 1798, also illustrate the point of view taken by many at that time.

Vol. I, p. 15. "It is to the power by the energy of which every living system is protected and preserved from decomposition and decay, and by which the different substances it receives are assimilated and changed, that I attach the idea of Life."

Again, on p. 330, of Vol. I, we read: "And finally that the gastric juice possesses, the power not only of killing living, but of reanimating dead matter, was proved by some experiments made, I believe, by Mr. Hunter and Spallanzani. They thrust pieces of putrid flesh, tied by a string, into the stomach of some dogs; and after leaving it some time in that organ, they withdrew the meat; and found upon exam-

[10] See Fordyce: A treatise on the digestion of food. London, 1791. Page 170. "But in the same manner the action of the powers of the stomach, and other organs of digestion, upon the food, is necessary for those powers which occasion its decomposition and recombination to act, so that, although they are always present in the substances capable of being converted into chyle, yet nevertheless they are not exerted unless they are influenced by the action, or circumstances which they meet with in the organs of digestion of a living animal; so that no chyle ever has been, and most probably never can be produced, excepting in the organs of digestion of a living animal."

ination, that from being offensive it had become sweet, from being putrid it was fresh again. It is not, therefore, sufficient for the food, by the organs of sense to have been selected, by the teeth to have been comminuted, by the mouth to have been masticated, by the saliva to have been blunted and blanded : it is by the active energy of the stomach alone, and the fluid it secretes, that it becomes digested and assimilated, that solid food is reduced to a fluid state, that it becomes killed as it were, and loses its old life, and then is animated anew, receiving from the living power of the gastric, the participation of life from the system to which it is applied." He adds in a foot-note : " That the food we receive must be killed by the stomach before it is vivified afresh is evident, from hence : If it retained its own living power in an eminent degree, it is possible to conceive that it might inosculate with the stomach, instead of being digested by it ; and if it retained its living power without inosculating, the nature of that food would be always apparent : we should participate of the quality of the beasts on which we feed, and of the vegetables also." I purposely refrain from extending these quotations by referring to the part which a vital principle, under various names, was playing at this time in the views of the best thinkers on the Continent.

It must not be supposed that the unsatisfactoriness of these arguments has only been recently recognized. I will spare the reader quotations which would demonstrate that quite early in the present century the " vital principle " was considered a vague and insufficient explanation of the difficulty.[11] It was not, however, until the second half of the century

[11] In Bostock's Chapter on Digestion, in Todd's Cyclopædia of Anatomy and Physiology, 1836-39, Vol. II, p. 23, he will find : " With respect, therefore, to the hypothesis of a vital principle, as maintained by Fordyce and many of the modern physiologists, we should say that it is rather a verbal than a real explanation of the phenomena, and that it rather evades the objections than answers them." See also : An Elementary System of Physiology. By John Bostock. Vol. II, (Boston reprint, 1828), p. 409.

had begun that an experimental refutation of John Hunter's theory was made — at least so far as it concerns the question now under discussion.

It is only about thirty years ago, the reader will remember, that Claude Bernard [12] found that gastric juice, injected under the skin, digested the subcutaneous tissues. He saw further, that the legs of a living frog inserted in the gastric fistula of a dog, were digested off to a great extent in about three-quarters of an hour, the rest of the frog remaining alive. A similar experiment was made with snakes. These observations were confirmed by Pavy,[13] Harley,[14] and others; they were extended by the partial digestion of the ear of a living rabbit. It thus became evident that the "life" of the animal could have but little to do with the protection of its digestive canal from proteolytic changes. The "external and extreme parts" did undergo digestion and the animal was not obliged to die, the very thing Hunter said could not happen.

Frenzel suggests that these experiments really only showed a partial solution of the "living tissues" and did not absolutely demonstrate their digestion — that is, their peptonization. He accordingly tried an artificial digestion of "living" tissues and arrived at interesting results. Several years ago I made a number of similar experiments and reached generally the same conclusions as those now printed by Frenzel. I reported my work at a meeting of the Boston Society of the Medical Sciences in the spring of 1883, but published nothing. It seems desirable to note them now as confirming the work of Frenzel and somewhat

[12] Claude Bernard: Leçons de physiologie expérimentale. Paris, 1855-6. Vol. II; Cours du semestre d'été, 1855, pp. 408–9.

[13] An account of Pavy's experiment with the ear of a rabbit, as well as his views concerning the protection afforded by mucus or epithelium, and the importance of the alkalinity of the gastric walls may be found in his "Treatise on the Function of Digestion," London, 1867, p. 74. The reader may also consult Pavy's paper: "On the Immunity enjoyed by the Stomach from being digested by its own Secretion during Life," in the Transactions of the Royal Society for 1863.

[14] Harley, loc. cit., p. 211.

extending it, and I do so without intending to claim any priority for the method or the results.

Frenzel's experiments were made by fastening a frog on a forked board so that each leg hung in a vessel which contained hydrochloric acid (0.2 per cent.) or acid and pepsine. In the latter case marked changes were soon observable. The skin freed itself in patches and the flesh gradually disappeared especially on the parts where the epidermis was removed. In such places the bone was fully exposed in about an hour and a half. The bloodvessels were also affected; the walls burst, the blood exuded and coagulated, and the coagula were finally dissolved. On examination the liquid in which such a leg hung was found to contain peptone — there had been a genuine digestion. The other leg, hanging in acid alone, is said to have shown no special change save that the outer layers of the epidermis were slightly swollen. Where the epidermis had been removed a swelling and softening of the muscles was not observed — nor could such a leg be afterwards digested by pepsin in a neutral solution as would be expected had the muscles imbibed the acid. It should be added that the experiment was carried on at a temperature of 38° C. Frenzel does not say positively that such frogs remained alive, but it is to be inferred from the tone of his article that they did. He also reports that merely moistening an exposed muscle "at a suitable temperature" suffices to bring about an evident digestion. The number of experiments is not given.

My own observations were made on a large number of frogs; altogether about fifty of them participated in perhaps twenty experiments, but some died too early to make their share complete and useful. A detailed account of the methods employed and of the changes perceived may be omitted now, and I will generalize them as much as possible. Originally I only intended to modify Bernard's method for lecture

purposes, and the lower legs of the frog hung in test tubes which stood in the water bath whose temperature was fairly constant (38° C). I was thus able to demonstrate that the lower legs could be much softened (or even drop off) and the rest of the frog remain alive — that is to say, the heart was still beating and the muscles of the upper leg responded perfectly to electrical or mechanical stimulation of the nerves. My occupations at the time unfortunately obliged me to leave the experiment unwatched over night. The results which this long exposure to acid alone produced differ from those of Frenzel in that the muscles were often much softened and even dissolved, but this effect was usually not so intense nor so extensive as where the leg was exposed to acid and pepsine. When, however, such solutions were compared, that produced by the aid of pepsine acquired a rose color with soda and cupric sulphate which only gave a purple color where acid alone had been active (Biuret reaction). In other words only the pepsine solution appeared to have really peptonized the muscle. Early in this work it occurred to me that the exposure to so high a temperature could not be a matter of indifference to the tissues. The frog is accustomed ordinarily to surroundings where the thermometer stands hardly ever higher than 15–18° C., and to remove him (or only his legs) suddenly and permanently to a climate where the mercury is always at 38° C., means a change such as would cause us much concern were we to make it ante mortem.[12] I accordingly repeated the experiments at room temperature with substantially the same results. Later, further modifications were introduced to lessen the possibility of disturbing the blood flow and the nutrition of the muscles by the hooks and bands which were needed to support the

[12] This objection does not seem to have occurred to Frenzel. Pavy, however, may have had it in mind when alluding (loc. cit. p. 74) to "the more powerfully acting stomach of a warm-blooded animal like the dog," as the weak point in Bernard's experiment with "a cold-blooded reptilian animal."

frog comfortably. Cutting the medulla oblongata as well as section of the sciatic plexus was tried, but the outcome of the experiment was the same and in general accord with Frenzel. I may add that control experiments were always carried on at the same time. Finally I followed a suggestion of Dr. H. P. Bowditch and curarized the animals, which enabled me to place the lower legs in little troughs containing the digesting solution. In this way it was chiefly the gastrocnemius muscle which was exposed to the liquid, and this was favored by slitting the skin. By this means I was able to reach some very interesting results. It proved to be possible to digest (or at least make translucent and soft) a good portion of the exposed gastrocnemius, while all the rest of the same muscle was uninjured. That is, the undigested portion was firm and red as in health, and still manifested that perfect irritability which belongs to a sound muscle. It is hardly necessary to add that the other muscles of the leg, the heart, in short, all the rest of the frog remained fully alive. This took place too, it must be remembered, at a temperature in no way unfavorable to the animal's existence or comfort. A more instructive form of the digestion of "living" tissues cannot easily be found. On varying the strength of the acid it was seen that solutions ranging from 0.3 per cent. to 0.05 per cent. were positive in their results. No decided effect, however, was produced by a mixture of pepsine with 0.015 per cent. HCl. which was competent to digest boiled fibrin. It thus appears probable that a local digestion of a living muscle may be produced by pepsine and an acid of such strength that the entire amount of acid employed is less than that which the blood might be expected to neutralize. While I cannot maintain that my experiments were sufficiently numerous to settle this point, especially as I did not have this particular question in mind at that time, the notes made as the experiments progressed suggest a conclusion of this character. I purpose ex-

amining this point more exactly when I can find time for such work.

I also tried to attack the living muscles in an alkaline menstruum by means of such pancreatic extracts as we then had in the laboratory. The results were either negative or inconclusive, but the ferments at my disposal were not as good as we now have, and I consider this question open for further investigation.

Finally, then, we must admit that we are still far from a satisfactory explanation of the immunity of the various digestive organs with reference to their own ferments while "alive" and the lack of such protection when "dead." It might be suggested that many or all of the ferments come from their glands in a partially inactive condition (in form of a zymogen, as pepsinogen, trypsinogen and so on), but this consideration would have value only for the glands, and is useless for the stomach and intestine. Frenzel suggests, as Krukenberg [13] had already recently done, that the comparative physiology of digestion may be expected to solve our problem. Possibly the solution will prove to be less simple than we expect, and by showing us how exceedingly varied in principle the processes are which we have been accustomed to lump together under a single name as "digestion," also demonstrate that the safety of the "living" structures immediately involved is due to equally varied causes. Of course no one supposes that the tissues actually remain "alive" when the digestion begins. That part which is to be dissolved "dies" either before or during the digestion, but the direct cause which changes the living complex albumin molecule with its vigorous resistance to dissolution into some feebler form making it the victim of any enzyme which may happen to meet it, no man knows with certainty or completeness.

[13] Krukenberg. Die eigenartigen Methoden der Chemischen Physiologie. Heidelberg, 1885, p. 20.