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Original Articles

OBSERVATIONS RELATING TO THE NATURE OF ATROPHY OF INTESTINAL ORIGIN.

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General atrophy that is associated with, and apparently stands in direct relation to, a greater or lesser degree of preceding intestinal disturbances occupies a position of profound importance in the pathology of infancy. Marasmus is, indeed, so common and often so intractable that the laity are almost as familiar with its general features as are physicians. Much less commonly, but still occasionally, a condition that is, in its chief clinical features, apparently the same as the atrophy of infancy, appears in early childhood. In later life, typical cases of this kind are rare; there are, however, very many instances of serious disturbance of general nutrition that seem to bear a direct relation to intestinal trouble, but are too pronounced in their general features to be satisfactorily explained by the mere loss of nutriment that occurs through lack of digestion and absorption—for these patients may still be absorbing an amount sufficient to maintain or improve nutrition, and yet they emaciate or remain about stationary in a condition of more or less profoundly depraved general nutrition. Cases of this kind have recently been studied by Roehl, who decides that the disturbance of nitrogen absorption does not suffice to explain the tissue loss; and the general absorption is at times quite sufficient to cover their needs.

THEORIES REGARDING ATHREPSIA.

An immense amount of work has been devoted to the study of the pathogenesis of infantile atrophy, particularly, but no satisfactory explanation of the nature of the condition has been furnished. It has been shown that digestion and absorption are impaired in most or all atrophic infants, but the degree of impairment is often by no means enough to explain the atrophy. I have myself, with Dr. Caspar Miller, studied the absorption in several such cases, and while it was below normal, it was not exceedingly bad and the infants still absorbed an amount sufficient to have made most of their contemporaries gain in weight and health.

The lesions found at autopsy are, too, insufficient to explain the condition. There is still a somewhat general belief that an extensive primary atrophy of the intestine occurs in these cases; but while this has repeatedly been described and has been considered the cause of the general emaciation, it has been shown by Heubner, Gerlach and Habel that the appearances on which so much stress has been laid are really due to the

manner in which the intestinal wall is prepared and cut for microscopic examination. Wentworth's recent able review of the pathology of the condition leaves only a single fact undisproved—Bloch found in several cases an absence of the granules that are normally present in Paneth's cells.

The hypothesis has also been put forward (Escherich) that the disorder may depend on the ferments and other obscure biologic elements in human and animal milk. This, however, could not explain the matter, for it leaves out of consideration the fact that athrepsia occurs in only a portion of artificially fed infants and not in all.

Recently a suggestion of another kind regarding the nature of the condition has been put forward. Since the injection of animals with protein of foreign species is followed by the development, in the blood serum of the animal injected, of substances capable of precipitating the protein that was introduced, Moro and Hamburger have attempted to show that the serum of atrophic infants contains a precipitin for cows' milk—thinking that they could in this manner demonstrate that foreign protein (namely, bovine casein) reaches the circulation in such cases. If this were the case, it might be conceived that this foreign protein produces chronic toxic symptoms that lead to emaciation, even though sufficient food be absorbed. They were not successful in their work, but Moro has recently found such a precipitin in one case. He declines, however, to draw any conclusions from this as to the nature of infantile atrophy. Even if such a precipitin is frequently to be found its presence may, I think, be quite as properly, if not more properly, applied in another way, in support of my own working hypothesis regarding the nature of infantile atrophy, which hypothesis I shall describe.

RECENT VIEWS OF PROTEIN DIGESTION.

I shall first, however, in order to make the character of my conception clear, find it necessary to refer very briefly to some of the recent transformations of view concerning the nature of protein, and the manner in which it is digested and utilized by the tissues, and shall refer also to some points in regard to ferments. All these matters are well known to those that have had particular interest in such questions, but are not yet generally appreciated.

The comparatively simple teaching of a few years ago, when put into its briefest form, was that the digestion of protein consists essentially of hydrolysis into albumoses and peptones, and the formation of small amounts of some simpler bodies—chiefly amino-acids, such as leucin and tyrosin, and that the albumoses and peptones are absorbed and, in the process of absorption or very soon after this, built up again into native protein. The process as conceived at that time was, therefore, in the main part merely hydrolysis of higher protein to lower forms of protein—the major portion of the substance

remaining protein all the time, and the chief apparent purpose of digestion being to transform the ingested protein into substances that are relatively very soluble and that easily pass animal membranes; that is, to get them into a form in which they can readily reach the circulation.

Throughout recent years, however, it has become increasingly evident that the change is much more fundamental than this; and the key to the understanding of the main purpose of digestion seems to have been furnished by more elaborate study of the products of digestion, and particularly by a more intimate knowledge of the composition of protein. That is, it has been shown that a protein consists of a union of numerous crystalline substances which are relatively simple in their structure as compared with protein, but still somewhat complex; these are chiefly or entirely so-called amino-acids, among the many of which leucin and tyrosin are the most popularly known representatives. Protein substances of different kinds contain varying amounts of the various amino-acids, but they differ quite as much in the quantity as in the quality of the component substances. Some forms of protein do contain some kinds of amino-acids that other protein substances do not, but the distinction between different protein substances seems to lie quite as much, if not more, in the fact that this one contains more of certain amino-acids, that one contains less of these amino-acids but more of others. To use the picturesque simile employed by the Germans to describe the matter, proteins are constructed of "buildings stones," and stones of many shapes are used in building any protein; but the ultimate structures differ in their architecture, and in giving them their proper form, sometimes more stones of one shape are employed, sometimes more of another.

Concurrently with the development of the above mentioned knowledge, it has been shown that the digestive breakdown of protein is much more complete than was previously taught. Even pepsin can carry a large part beyond the peptone stage, and trypsin does this much more quickly and extensively than pepsin. Trypsin, indeed, is capable, even in laboratory experiments, in some circumstances, of carrying the whole amount of protein beyond the peptone stage; and, hence, under the more favorable conditions that exist in the animal organism, it probably carries most, possibly nearly all, beyond that stage.

At the same time, it has been made apparent that the intestinal mucous membrane contains a proteolytic ferment which has been given the name erepsin. Whether this has the characteristics attributed to it by Cohnheim—namely, inability to attack native protein, but active powers of further fragmenting albumoses and peptones—or whether, like trypsin, it can carry on the process from the beginning, is a question that is still *sub judice*. Of the existence of a proteolytic ferment in the intestinal mucous membrane, there is, however, no question; and there is every probability that it is produced there, and is not simply pancreatic trypsin that has lodged there.

It seems at present that the purpose of digestion is to fragment the protein complex thoroughly into its constituent amino-acids, or building stones; and that the protein falls first into the hands of pepsin, then trypsin, and next the ferment of the intestinal mucous membrane, in order that with each attack the fragmentation may be made more complete. It is not yet clearly determined whether these ferments actually differ, as they

have been supposed to do, in the nature of the end products that they produce. The progressive action of one after the other may be intended simply to permit each succeeding ferment to put finishing touches on the portions of unfragmented or partially fragmented protein that have escaped the preceding ferments. The prime object of this breaking-up process appears to be to yield the amino-acids themselves; in order that they may be available in free form and in proper quantities, for a complete reconstruction, which will yield protein homologous with the individual to be nourished. It is not necessary to fragment all portions completely as certain fractions will be obtained that can be reconstructed into homologous forms without complete fragmentation, but except for such fractions it must be complete. That the digestive process, together with the subsequent reconstruction process, does accomplish this transformation—that is, that it does change protein of foreign species, containing certain amino-acids in quantities peculiar to this protein, into another form of protein, apparently containing the same amino-acids in quantities peculiar to the individual that has digested and absorbed the protein—has been shown experimentally with almost final positiveness; and it has likewise been shown that the reconstructive process occurs before the absorbed digestive products reach the general circulation, almost certainly, indeed, in the intestinal wall itself.

Furthermore, physical chemists consider it to be theoretically well nigh certain that the same ferment that accomplishes fragmentation also causes the reconstruction—that the direction in which a ferment acts, whether toward the production of simpler products or toward the formation of more complex substances is determined, not by the nature of the ferment, but by the physical and chemical conditions of the medium in which it acts and by the concentration of the products of digestion. If conditions favorable to disintegration are present, the ferment hastens this; but if the conditions favor synthesis, the same ferment hastens this. This has actually been shown to occur with some ferments that act on carbohydrates and fats; and similar observations that are suggestive, though not yet conclusive, have been made regarding proteolytic ferments. The conditions of such experimentation with the latter ferments being much more difficult than those attached to carbohydrate and fat ferments. If this view that ferments are capable of reversed action is correct, as a general principle, and this now appears most probable, the same ferment in the intestinal wall that continues the process of fragmentation of the protein food also carries on the process of reconstruction of homologous protein.

This cursory statement of some of the main aspects of the present day teaching of the physiology of digestion will, I trust, suffice to make clear the hypothesis that led to the observations I am about to report. My results have not yet been sufficiently extensive or elaborate to justify, of themselves, quite so formidable a preamble as I have given, were it not that the explanation is necessary in order to make their bearing clear. So far as they go, however, they offer some support to the following hypothesis:

THE AUTHOR'S HYPOTHESIS.

Clinically, it is quite clear that most atrophic infants do well, provided they are not already far advanced toward death, if human milk can be given them; while with even the most capably conducted artificial feeding,

they usually have, at best, a precarious and long struggle for existence, and very often go slowly, but persistently, toward death. It seems, then, that the difficulty consists in making use of milk of foreign species. The difficulty does not lie simply in accomplishing the absorption of the elements of the heterologous milk; for, as I have already noted, sufficient is absorbed in many of these instances to produce a gain in other infants.

It has seemed to me that the disturbance may be the result of disorder of the ferment function of the intestine. That is, when the protein of the food is progressing in the course of its breakdown the final attack by the ferment of the intestine does not occur or is ineffectual; that the protein complex is torn apart more or less completely by the pepsin and trypsin, but that fragmentation sufficiently complete, in order that the structure may be rebuilt in a new form entirely homologous with the patient's tissues, does not take place.

Granting the absence or serious reduction of this ferment in cases of atrophy, one of two things may be conceived of as occurring as a consequence: in the first place, it might be that the protein would be fragmented to various stages short of absolute completeness—to albumoses, peptones, simpler non-protein amino-acid complexes (heptides) and in more or less considerable extent, to free amino-acids—and that these would then be reconstructed; but the synthesis taking place without sufficient preceding fragmentation, the product of synthesis is not the normal one, but is more or less hybrid in character. To use again, for clearness of conception, the building stones simile, it would be like taking away the upper structure of a building, while leaving the foundation unaltered, and then making the new structure conform to the old foundation, instead of tearing out the latter completely and building anew from the start. The infant would, in such a case, have his circulation and tissues supplied with more or less markedly foreign protein, while normal infants receive homologous protein. The infant nourished with mother's milk, even though he absorbs all his protein food wholly unfragmented or only half fragmented, would not so far as we know, be crippled by this, for his food protein is already homologous. The artificially fed infant that I have postulated, however, who receives imperfectly broken down, and hence improperly reconstructed protein, has manifest difficulties in his way in carrying out metabolic processes; and the most evident difficulty would be in tissue construction. He would be able to use much, at least, of the more or less completely foreign protein in obtaining energy, that is, he would be able to disintegrate it, for it is known that animals can thus utilize considerable amounts of foreign protein when introduced subcutaneously or into the circulation. In attempting to use it to construct tissue, however, he would be obliged to go through the difficult task of disintegrating again, and then completely reconstructing it; while, when the tissues are, as is normally the case, served with homologous protein, it would seem evident that the process of construction and repair of the tissues would be comparatively easy. We have, indeed, no knowledge that the tissues are capable of building new tissue from foreign or partly foreign protein served thus directly to them, and it may readily be that they are more or less completely incapable of it. They can undoubtedly secure energy from it and can transform one variety of homologous protein into another variety of homologous protein, but this is very different from transforming a foreign protein into a homologous

protein. Even if they could do the latter, to impose on them the necessity for carrying it out would be to make entirely unnatural demands of them, and they would doubtless be likely often to fall under the extra burden.

The second idea conceivable as the result of absence of the intestinal proteolytic ferment is dependent on complete acceptance of the theory of reversibility of ferment action. While this theory now appears to be probably susceptible of general application, this has not been actually demonstrated to the same extent as have the other matters that I have so far used in constructing my hypothesis. Therefore, although this theory will probably be shown to be correct, I mention its relation to the subject under discussion in only a secondary place. In case it applies in this instance, the effect would appear to be that, the intestinal ferment being reduced or absent, not only would disintegration of the protein suffer, but the especial agent that carries out the reconstruction of protein being decreased or absent, the reconstruction also would be more or less completely absent. Instead, therefore, of entering the circulation as hybrid reconstruction products, the more or less completely fragmented products would themselves go into the circulation, and use of them by the tissues, in the synthesis of new tissue, would be much the same difficult process as in case they had been made into hybrid protein.

Either of these ideas would be in harmony with the repeatedly mentioned fact that absorption in many of these cases is sufficiently good to maintain nutrition; for incomplete fragmentation would not prevent absorption, since digestion products, all the way from albumoses on, are readily capable of absorption—and indeed, this occurs with many unchanged albumins. The hypothesis would in either case, also, be in harmony with—indeed, it is dependent on and, if correct, explanatory of—the fact that the difficulty lies in the utilization of milk of foreign species. There is no good evidence that infants ever fail to assimilate human milk, unless they are already desperately ill; provided that the milk is not so rich in some of its constituents as to upset digestion or so poor as to be insufficient; and provided, also, that the mother or nurse supplying the milk is not the subject of physical or emotional disturbances that presumably cause the quality of the milk to be disordered. In other words, there is no evidence that an infant, not desperately ill, that is taking normal human milk of such composition that it does not disturb digestion, ever fails to be able to utilize this milk on account of the character of its constituents. On the other hand, large numbers of infants, when fed on foreign (that is, usually cows') milk, even when the constituents are of wholly normal quality, do badly or die, however one may vary the proportion of the constituents in deference to difficulties in digestion; often, indeed, even when no noteworthy difficulties in digestion are present. The experience of Westcott, Holt and others, shows that many malnourished or even severely atrophic infants that do badly on cows' milk mixtures exhibit remarkable improvement if, while their diet still consists chiefly of the same mixture, small quantities of human milk are added. This suggests strongly that they can secure from the artificial food the energy that they need, if only the essential moiety absolutely demanded for tissue-building and repair is given them in normal form.

The hypothesis also conforms with the fact that infantile atrophy, as well as the malnutrition of older children and adults, is not a clearly delimitable condition. There is no definite boundary line on one side of which

cases are simply malnourished, while on the other side they are the subjects of persistently progressive atrophy; nor are there any cases that can be labeled essentially fatal. The worst of them almost may get well if only one can secure a food that is especially suitable in the particular case. If in such cases human milk is used improvement is often remarkably rapid, while on other foods it is, as a rule, slow and laborious at best. The hypothesis that I have described does not conflict with these facts, but is rather supported by them. Such variations in the severity of atrophy may be chiefly a question of a larger or smaller degree of reduction of the ferment action of the intestine. It is not to be expected that the ferment or ferments would often be entirely and persistently absent; it is rather to be expected that various degrees of reduction of the amount or the activity of the ferments would occur in different cases, and that there would correspondingly be more or less severe results. Since there would be no essential structural change in the intestine, but simply more or less complete failure of a function—a function, however, that would seem to occupy a critically important position in the process of homologizing protein—any little increments added to the powers of the patient to carry on functions properly (such increments as would be secured through better feeding and better hygiene, and the consequent better general nutrition) would improve the manufacture of ferments, as well as other functions, except in cases so badly damaged that the recuperative powers were lost.

The general line of thought that I have indicated, whether my hypothesis is correct or not, would also offer a reasonable explanation of the fact that extreme grades of atrophy are so much more common in very early life than in older persons. After growth is completed, synthesis of tissues is necessary only in so far as repair is required; while in the young not only is repair required also, but there is, in addition to this, a relatively enormous amount of synthesis necessary in manufacturing new tissue. Any disorder that makes synthesis of tissue more difficult would consequently fall particularly heavily on the young.

I would likewise note that the one point regarding the pathology of infantile atrophy that is as yet unsailed (Bloch's observation that granules are absent from Paneth's cells) seems to me to suggest of itself that the ferment functions of the intestine may be at fault. Similar granulations are observed in other digestive organs, when they functionate normally, at those times when they are preparing their digestive secretions; while after the secretions are discharged the granules become much reduced in number or entirely absent. Lack of granules from the cells in the intestines of atrophic infants may, therefore, readily mean that these cells are not producing digestive secretions, while the same cells do produce them in other infants.

I have previously mentioned the possible presence of precipitins for bovine casein in the blood serum of atrophic infants. This matter is not of much importance in this connection, as there is little evidence as yet that such precipitins exist. If they do exist it is apparent that their presence is quite as directly in conformity with the view that I have outlined as with the suggestion that a chronic toxic state results from the presence of the foreign casein in the circulation. Those that have experimented on the effect of subcutaneous injections of unaltered foreign protein differ in their conclusions; but it may, I think, be said fairly, so far as this concerns

the question immediately under discussion, that atrophic infants show absolutely no clinical evidences of any such actively toxic state as has been described by some authors as consequent on the subcutaneous administration of very small amounts of foreign protein. Yet if such infants do have casein-precipitins in their blood, they must absorb directly quite as large amounts of casein as are used in injection experiments. This point seems to me to rob the theory of a foreign-protein intoxication of its chief established basis, so far as infantile atrophy is concerned; although I, of course, do not deny the possibility that such an intoxication may have something to do with the condition.

CASES STUDIED.

Up to the present, my studies regarding the defensibility of my hypothesis have consisted of investigation of the proteolytic power of the intestines obtained at autopsy in eight cases. Three of these cases were characteristic instances of progressively fatal atrophy (two in infants and one in a child of two years); three were cases of advanced emaciation that was known to be due to other causes than simple atrophy, these cases serving as controls; and the other two cases were instances in older persons of continuous and finally extreme emaciation for which autopsy showed no cause.

Although I have been working on the question, as opportunity offered, for a year past, the number of cases that I have to report is small, because I have, in order to avoid confusion, limited my observations relating to the atrophic cases carefully to those in which the clinical conditions and the autopsy findings showed an entire absence of evidence of infection of the digestive tract, and in which, also, there was absence of evidence of poor absorption or of a noteworthy degree of gastroenteritis. I have found it difficult to secure such material from entirely reliable sources. The three cases of infantile atrophy that I report were, however, of this kind. All showed at autopsy merely the lesions of simple, uncomplicated atrophy, and clinically, all had shown merely progressive wasting, with no gastric symptoms. Intestinal symptoms, also, were absent in all except Cases 2 and 3, in which two or three bowel movements occurred at times in the 24 hours. The movements, however, were not large, appeared well digested, were of good color, and did not contain visible mucus.

Case 1 was under the care of Dr. Howard Hill, who did the autopsy. Cases 2 and 3 were under Dr. J. P. Crozer Griffith's care at the Children's Hospital, and Dr. C. Y. White and Dr. Howard Carpenter made the pathologic studies in them. For the material from the other cases, I am indebted to Dr. Longcope and Dr. Lavenson. I wish, also, to acknowledge my especial indebtedness to Dr. Ralph Pemberton for aiding me in the studies of the cases. The details of the methods used will be given later with the figures obtained. Meanwhile, I shall briefly discuss the results.

In the first of the three cases of infantile atrophy, the proteolytic ferment in the intestinal mucous membrane was present in extremely small amount, if at all; in the second it was greatly reduced as compared with the three control cases; in the third case, which was the most rapid in its progress, the infant dying at five months, no ferment-action was demonstrable. In the first of the two cases of emaciation of undetermined cause in older persons, ferment-action was exceedingly slight, in the second of these cases it practically could not be demonstrated at all. Indeed, in the whole group of five atro-

phic cases, all those that show slight ferment-action provide, to indicate this, figures so small as to be almost or quite within the range of error. Since, however, in all instances, two nitrogen-estimations were, as is usual, made for the purpose of controlling the results; and since, in all instances (except case 5, in which the control was lost), the two estimations corresponded practically exactly, I think that the figures are accurate, and do not indicate slight ferment-action.

The figures from the three control cases that had not simple atrophy do not, to be sure, indicate the digestion of large absolute amounts of protein; but they do show relatively large amounts as compared with the atrophic cases, and it must be remembered that I was dealing with small figures in all cases, since, as may be seen in the protocols of the experiments, only 10 c. c. of milk was introduced in each instance for the ferment to act upon, in addition to the small amount of protein present in the extract which contained the ferment; and the amount of milk mentioned represents only about 0.05 grams of nitrogen. Considering that the period of digestion was purposely made short (only four hours), in order to be more certain of excluding bacterial action, the figures in the non-atrophic cases really show a very considerable degree of digestion, while the atrophic cases, at best, show almost none.

The objection may be offered that the differences were due to bacterial action. Toluol was used freely, however; the experiments were made so short that there was little opportunity for bacteria to act; and, more important than this, there are no irregularities in the results to suggest that bacteria had been active. It is, perhaps, impossible in experiments carried out as these were with an extract of the mucous membrane, to exclude bacterial action absolutely. I used this method, however, instead of attempting to isolate the ferment by means of precipitation and dialysis, because I believe that it is possible only by means of the method followed to secure quantitative comparisons in different cases; and bacterial action cannot be said to have produced the results obtained, unless one assumes the rather strained position of considering that bacterial proteolysis occurred regularly in the non-atrophic cases, while it was regularly absent or almost absent in the atrophic.

Leaving aside the two cases in older persons for the present, the bearing of the results in the three of infantile atrophy seems to me to be the following: So far as these cases go, they harmonize with the hypothesis that I have stated, since they demonstrate that in these cases there was great reduction or entire loss of proteolytic power in the intestinal mucous membrane. It may readily be thought that this was a mere secondary effect of the profound emaciation, but this appears decidedly improbable, when one considers the three control cases, all of which were extremely emaciated, but as the result of definite causes other than simple atrophy. These cases show very much greater proteolytic action than do the atrophic cases. It might be considered, also, that there was simply a general reduction in the ferments of the digestive tract. I attempted to exclude this objection by testing for pepsin in extracts of the gastric mucous membrane of the atrophic cases, and in all three instances I got a markedly positive result; hence pepsin was present in all.

Beyond what I have said, I do not think I can speak decidedly as to the meaning of my results. If continued studies shall show similar results consistently, this will demonstrate definitely a marked disturbance of the fer-

ment-function of the intestine, and will indicate strongly that this has an important primary relation to the atrophy. Further studies are necessary, however, in order to show that this is a constant condition in atrophy, and a condition that is usually absent in other cases. Furthermore, in addition to the line of observation that I have been following, it is important to determine whether the intestine does or does not, in these cases, retain its power to produce secretin and enterokinase, and thereby to excite secretory activity in the pancreas and to activate the pancreatic trypsin. It is likewise important to determine, if possible, to what extent the pancreas retains its functional capacity in these cases; although this is extremely difficult to do satisfactorily with postmortem material, because in extracts of the pancreas the trypsin becomes, to some extent, activated, and it is difficult to determine to what extent this occurs, and therefore difficult to secure reliable results in comparing different cases.

In spite of the fact, which I have repeatedly mentioned, that absorption in these cases often does not suffer enough to explain the atrophy, it may be that the pancreas, as well as the intestine, shows reduction, and perhaps, entire loss of ferment-function. We know now quite clearly that fat-absorption is sometimes good in the entire absence of pancreatic secretion; and it is quite possible that this is more largely true of protein than we have thought. Indeed, in many cases, with severe lesions of the pancreas, the nitrogen-absorption is known to be not bad. This possibility of disordered pancreatic function is of particular interest in infants; for there is some testimony, though not based on very good evidence, that in the first three months or so of life the pancreas has only a subordinate rôle in carrying on digestion and absorption, while after this it becomes increasingly important. Athrepsia in infants is particularly likely to begin about the third month of life; and, hence, if the above-mentioned view is correct, it becomes possible that the difficulty in athrepsia may be partly, at least, the result of failure of the pancreas to take up the large function that it should assume. If the pancreas fails to do its duty, fragmentation of the protein-molecule will be still more incomplete than if the intestinal ferment only were absent. In this case, pepsin alone would be left to digest the protein sufficiently for its absorption; but in infants, at any rate, with their simple milk diet, it is probable that pepsin is capable of doing at least a very large part of this. If there is any truth in the view that I have just noted concerning the development of the pancreatic function in early life, pepsin must, in even normal infants, in the very early weeks of their existence, do most of the work except that carried out by erepsin.

In addition to what I have mentioned, it is desirable to attempt to determine whether amino-acids or peptides do escape into the circulation in these cases; or whether, on the other hand, the circulating protein of atrophic cases shows differences from the circulating protein of other cases. These last points are very difficult to determine with our present methods, particularly with the paucity of material provided by the cadaver of an athreptic infant. They may be possible of solution in cases of atrophy that occur in older persons, perhaps even during life.

Furthermore, it is desirable to determine whether there are alterations in the ferments in the tissues that lie beyond the digestive tract.

Finally, I would, with an equal consideration of the

criticisms that I have put upon my previously-mentioned results, refer to the two cases in older persons, as they need brief separate description. The first of these, Case 4 in the protocol, was an instance of dementia præcox in a man of 27, who was under the care of Dr. Charles W. Burr at the Philadelphia General Hospital. The only noteworthy points in his history were that, after prolonged overwork, he had developed delusions of persecution; and this had been followed by a stuporous state. He was admitted in the latter condition; and for eight months afterwards, remained in a state of complete apathy, or negativism, physically and mentally. Throughout this time, he was unresponsive and practically motionless. He was fed continuously through a stomach-tube, on about three quarts of milk and eight eggs a day; but in spite of this he emaciated constantly and finally to an extreme degree. He then came out of his stupor rather suddenly, took an interest in his surroundings and ate with appetite. Though he then took no food beyond the ordinary ward diet (and this is certainly not more than what had been given him before, but rather less), and though he was in this period moving about and doing a little work, while previously he had been absolutely quiet, during the next three months, he gained flesh rapidly and became actually fat. He then went into stupor again, and remained so for two years and ten months, until he died. Throughout this entire time, he had been fed on the previously mentioned amounts of milk and eggs, through the stomach-tube, and during this period he again emaciated progressively, and ultimately to the last degree.

Case 5 was a patient of 25 years, who had meningitis followed by hydrocephalus, lasting seven weeks. During this time he was stuporous and during the last three weeks he was fed through a stomach tube. He emaciated rapidly and finally to an extreme degree, in spite of the subsidence of any evidences of infection.

Both these cases, as I have stated, had practically no evidence of the presence of proteolytic action in extracts of the intestinal mucous membrane. I would note also that in both, contrary to the conditions in the infantile-atrophy cases, there was but faint, if any, evidence of the presence of pepsin in the extracts from the gastric mucous membrane. Neither case had shown any digestive disturbance during life, and neither had any lesions of the alimentary tract at autopsy. There was no direct occasion, therefore, for considering that the intestine was at fault in any way in these cases, but I studied them in this connection for two reasons: First, because they were instances of unexplained progressive emaciation; and second, because Pawlow, in discussing his celebrated work on the influence of psychic factors upon the secretion of digestive juices, suggests that the more or less profound disturbances of nutrition often seen in depressive forms of insanity may be, to some extent at least, due to the entire lack of psychic stimulus to the production of digestive ferments.

Two cases do not justify much comment. I would say only that they may, on the one hand, be evidence merely that my hypothesis is incorrect; that is, reduction or loss of the ferment functions of the intestine may occur in a variety of conditions and may have no primary relation to any disease or symptoms, and these cases are, perhaps, merely examples of that possibility. On the other hand, they may prove to have importance in explaining such conditions. In Case 4, especially, there was a striking succession of events, which appeared to show that the emaciation was closely related to the

stupor. This may mean simply that some intoxication or other obscure condition was the cause of both stupor and emaciation, but it may be that the whole disorder was nutritional—that depraved nutrition from overwork produced psychic depression, and the latter so largely depressed physical functions, among which is the function of elaborating ferments, as to cause the progressive general atrophy. The sudden alterations in both mental and physical condition that occurred in this patient and are common in similar cases is certainly quite as much in harmony with this view as with the theory of intoxication, for every one is familiar with the extremely sudden changes in the gastric secretion that are known to occur at times in cases of purely neurotic achylia gastrica.

I believe, therefore, that the emaciation occurring in depressed and stuporous states, and also other obscure forms of emaciation, are suitable subjects of study from the standpoint that I have indicated. I do not, of course, mean to suggest in the most distant way that emaciation in general is dependent simply and solely upon failure of intestinal ferments. I mean merely that lack of these and of other ferments may be an important element in cases of this sort, and since the proteolytic ferment of the intestinal mucous membrane, according to prevailing views, seems to occupy a conspicuously important position in the process of utilizing protein, it is possible that more or less complete absence of this ferment, owing to the disordered chain of events that would probably ensue upon its absence, may be one of the important elements in explaining some instances of progressive emaciation, and, too, of chronic, but stationary, depraved nutrition. It is also possible that at times lack of this ferment is the chief and, indeed, of itself a sufficient, explanation of the nutritional disorder.

THE AUTHOR'S METHODS.

The methods used in my work were as follows: The whole of the stomach and small intestine was secured directly after the autopsy. This means from 12 to 18 hours after death, but a delay of this length appears from Vernon's observations to cause no decrease in the amount of erepsin. There was some difference in the time that elapsed in the individual cases between death and autopsy, but this was, at most, a few hours, and the average time in the atrophic and non-atrophic cases was just about the same. As soon as they had been secured, the stomachs and intestines were very thoroughly washed with running water. In obtaining the extracts the mucous membrane was scraped off the entire surface of the stomach or small intestine, whichever was being worked with; the whole amount obtained was thoroughly mixed and weighed portions were taken. Scrapings from the entire mucous membrane were used because the amounts of pepsin and erepsin, respectively, in different portions of the stomach and bowel differ largely; and in using organs from subjects of different ages and sizes, it would be impossible to be certain that exactly similar portions had been taken if one simply cut out especially chosen parts and took the scrapings from these.

Of these mixed scrapings from the intestine, a weighed portion was each time taken and ground for 10 minutes in a mortar with sand. The ground scrapings and sand were then washed into a flask with Ringer's solution, using always 30 parts of the solution to one part of the scrapings. Toluol was then added; and the flask was stood aside for four hours, shaking it every 20

minutes to half an hour. The contents were then strained, each time in the same manner, and 50 c. c. of the strained fluid was introduced into each of two flasks. That in one of these flasks was immediately boiled for a moment and then cooled, and to each flask was added 10 c. c. of previously-neutralized milk, the milk being from a supply that is constantly under chemical supervision, and that I know from a large number of personal estimations to vary extremely little in its nitrogen-content. Toluol was then added to each flask and thoroughly shaken with the fluid, and both flasks were placed in the thermostat at body-temperature for four hours. Following Cohnheim's procedure, I then added 10 c. c. of saturated sodium chloride solution; boiled a moment; added 10 drops of acetic acid; boiled again; filtered and tested the filtrate to see that it was biuret-free. If it were not, or if it were not perfectly clear, it was filtered again, when it always became perfectly clear and biuret-free. The nitrogen in the filtrate was then estimated. The results gave the "uncoagulable" nitrogen, and the excess in the specimen that was not boiled in the beginning over that in the boiled specimen showed the amount digested. The figures given are for the whole amount in the flask.

At the same time that these flasks were prepared, two other flasks, each containing 25 c. c. of the extract from the intestinal mucous membrane (boiled in one; unboiled in the other) and 10 c. c. of a 1 per cent. solution of Witte's peptone, together with toluol, were placed in the thermostat for four hours, and afterwards coagulated in the manner mentioned, and the strength of the biuret-reaction in the filtrate was noted. The degree of reduction in the intensity of the biuret-reaction in the unboiled specimen, as compared with the boiled specimen, provided qualitative evidence of the activity with which the "peptone" had been digested beyond those bodies that yield a biuret-reaction.

I used cows' milk as the substance to be digested, because it is the food upon which artificially-fed infants depend. Even if Cohnheim be correct in claiming that erepsin can not digest most unchanged albumins, and that it is necessary that albumins be previously digested at least as far as the albumose-stage, casein is, nevertheless, an entirely appropriate substance to use in testing the activity of erepsin; for Cohnheim himself states that casein constitutes an exception to the above-mentioned rule, since, unlike most other undigested albumins, it is acted upon by erepsin. In case Cohnheim is right in stating that erepsin acts upon casein but not upon most other unchanged albumins, this of itself strongly suggests that the ferment may be especially important in infants whose diet is limited to milk. It was, indeed, this statement in Cohnheim's article that first brought to my mind the possible relation of this ferment to infantile atrophy. I have not, however, considered that the proof that erepsin can not act upon other albumins is sufficiently definite to make it justifiable to use this point in my argument, in the earlier part of this paper, in favor of my hypothesis.

The pepsin tests were qualitative only. The scrapings of the gastric mucosa were placed in one-twentieth normal hydrochloric acid, in the proportion of three parts scrapings to 200 of hydrochloric-acid solution, and allowed to stand until the next day, when the fluid was strained off. Of the strained fluid, 25 c. c. was introduced into each of two flasks, one of which was boiled and then cooled. To each flask I then added 10 c. c. of a mixture of one part of fresh white of egg in 10 parts

of one-twentieth normal hydrochloric acid. These were then put in the thermostat for four hours. They were then neutralized, 10 c.c. saturated sodium-chloride solution was added, the mixture was then boiled, rendered slightly acid with acetic acid, boiled again, then rendered slightly alkaline with sodium hydroxid, boiled again and filtered perfectly clear. The filtrate was then tested by the biuret-test and by precipitation with phosphotungstic acid. The bulk of the precipitate to the latter indicated the amount of digestion-products, and the intensity of the biuret-test indicated the same.

RESULTS.

CASE 1.—Atrophic child of 2 years, had been emaciating for a year after preceding digestive disorder. The filtrate from the two flasks containing intestinal extract gave, after digestion, the following figures for nitrogen:

Unboiled specimen.....	0.0200
Boiled	0.0191
Increase	0.0009

Witte peptone digestion: Boiled and unboiled indistinguishable in biuret test.

Pepsin Test.—Biuret entirely absent in the boiled specimen, decided in the unboiled. A slight precipitate to phosphotungstic acid in the boiled specimen; much more marked in the unboiled.

CASE 2.—Atrophic infant of six months; weaned at four months; very ill-nourished then and had grown progressively worse since: Erepsin digestion experiment.

Unboiled	0.0117
Boiled	0.0088
Increase	0.0029

Witte peptone digestion: Boiled slightly more marked than unboiled.

Pepsin Test.—A trace of biuret in the boiled specimen; marked reaction in the unboiled. Phosphotungstic precipitate slight in boiled; marked in unboiled specimen.

CASE 3.—Atrophic infant of five months; weaned at three months; emaciating continuously since: Erepsin digestion experiment.

Unboiled	0.0144
Boiled	0.0144
Increase	0.0000

Witte peptone digestion: Boiled and unboiled indistinguishable.

Pepsin Test.—Biuret absent in boiled specimen, distinct, but not very marked in the unboiled. Phosphotungstic precipitate very slight in the boiled; more bulky in the unboiled, but less marked than in the other cases.

CASE 4.—Dementia præcox: Erepsin digestion experiment.

Unboiled	0.0156
Boiled	0.0137
Increase	0.0019

Witte peptone digestion: Boiled and unboiled indistinguishable.

Pepsin Test.—A trace of biuret in both the boiled and the unboiled specimen; very slight in both, and no difference observable. Slight phosphotungstic precipitate in both; no marked difference.

CASE 5.—Hydrocephalus: Erepsin digestion experiment.

Unboiled	0.0182
Boiled	0.0179
Increase	0.0003

Witte peptone digestion: Boiled and unboiled indistinguishable.

Pepsin Test.—Faint trace of biuret in both the unboiled and the boiled specimen, and a very slight phosphotungstic precipitate in each.

CONTROL CASES.

CASE 6.—Infant of nine months, dead of general tuberculosis: Erepsin digestion experiment.

Unboiled	0.0306
Boiled	0.0112
Increase	0.0194

Witte peptone digestion: Boiled pronounced biuret, unboiled very slight.

CASE 7.—Infant of five and a half months, dead of slow starvation. (Extremely insufficient feeding by an ignorant mother; admitted moribund): Erepsin digestion experiment.

Unboiled	0.0215
Boiled	0.0147
Increase	0.0068

Witte peptone digestion: Boiled very distinctly more marked than unboiled.

CASE 8.—Adult, died in convalescence from typhoid fever, after a long illness and extreme emaciation: Erepsin digestion experiment.

Unboiled	0.0229
Boiled	0.0117
Increase	0.0112

Witte peptone digestion: Boiled marked, unboiled slight.

HEMOLYSIS IN PERNICIOUS ANEMIA, AUGMENTED BY URINARY RETENTION.

REPORT OF CASE.

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An article on "Recurrent Intermittent Retention of Urine Occurring with Remissions in a Case of Pernicious Anemia"¹ attracted my attention and led me to compare it with a similar case lately observed in the medical clinic of Professor George Dock. Dr. Cunningham's case was a male, aged 47, who had well-marked symptoms, physical features and a typical blood picture of pernicious anemia. In addition he had a history of retention of urine four years before, after which he was regularly catheterized for three months. At the time of his admission he urinated every two hours and was up more often during the night. In addition, difficulty in starting his urine and dribbling were complained of. Examination revealed a hypertrophied prostate, sufficient to cause frequent attacks of retention. Cystoscopic examination showed a chronic cystitis, and on draining the bladder as much as thirty-six ounces of residual urine were obtained. Bottini's operation was performed under cocaine anesthesia. In three months the patient had no urinary symptoms and his blood was in good condition. He returned because of the reappearance of the anemia one month later, and complained at the same time of urinary symptoms—namely, dribbling and difficult micturition. The residual urine had again increased. The bladder symptoms were relieved, and along with the improvement in his blood his urinary symptoms became better. In six months he had a similar attack and again recovered. Finally two years and two months after the onset, another attack came on from which the patient never recovered, dying from "uremia." In these numerous attacks the lowest blood count was 472,000, hemoglobin 10 per cent.; the highest 3,500,000, hemoglobin 45 per cent. The postmortem of the urinary system revealed chronic cystitis, hypertrophied prostate, dilatation of the ureters, kidneys, pelvis and calices. Urinary

findings at each examination were practically the same. The urine was pale, of low specific gravity and acid or neutral. There was a trace of albumin, but no sugar. There was always sediment consisting of pus, blood, and hyaline and granular casts.

In many respects the case I purpose to report herein resembles the one just outlined.

Patient.—M. L., aged 56, stonemason, American and single, came into the medical clinic on Jan. 4, 1907, complaining of numbness, stiffness of the hands and feet, diarrhea and loss of appetite.

History.—There was nothing notable in the family history. He had had typhoid at 15. He denied venereal diseases. Drank beer in moderation and smoked six pipefuls of tobacco daily. Five years previously, following exposure to cold and dampness, both shoulders became stiff, and there was some loss of power in his legs. The weakness persisted and this he noticed was more apparent on the least exertion. Diarrhea began two weeks before coming to the clinic, with from four to six stools per day. At this time he had grown dizzy and stumbled occasionally. His hands were numb and he found it impossible to button his clothes. He had had difficulty with urination for some time, but could not definitely remember the time of onset. In the early part of October he began to find it necessary to get up at night to urinate. Soon after this a burning pain at the beginning of urination and dribbling annoyed him. These symptoms became more pronounced so that when seen the patient urinated about every two hours and found it necessary to rise at least three times every night to empty his bladder. The urine was small in amount, pale yellow, and slightly turbid.

Examination.—Patient was of medium frame, skin dry, very pale, freckled and inelastic. There was a small amount of panniculus. The hair was scanty and gray. Height five feet eleven inches, weight 122 pounds. The pupils were equal and reacted to light and accommodation. The teeth were very poor, the gums were red and spongy, the tongue fissured, moist, glossy and tremulous. The mucous membranes were pale. The neck was symmetrical and the thorax of good length, breadth and depth. The clavicles were prominent. The apex of the right lung was lower than that of the left and there was relative dullness on the right. Over the dull area there was weakened vesicular breathing with prolonged and slightly blowing expiration. No adventitious sounds. Remainder of the lungs negative. The apex of the heart could neither be seen nor felt. The cardiac dullness was not enlarged. The first sound at the apex was weak but clear. The second sound was relatively louder and more abrupt. The second pulmonic was weak, distant and impure, and the second aortic was clearly heard. The pulse was full, quick, of good tension, and regular. Examination of the abdomen showed it to be pale, inelastic, walls lax and ribs and crests of the ilia prominent. Palpation negative. The prostate was enlarged, the right lobe being somewhat larger than the left.

Blood Examination.—Red blood cells, 2,220,000; white blood cells, 6,800; hemoglobin, 42 per cent (Miescher). Differential count of 500 cells. Small lymphocytes, 40.4 per cent.; large lymphocytes, 2 per cent.; polynuclear neutrophils, 50 per cent.; polynuclear eosinophiles, 5.4 per cent.; mast cells, 0.6 per cent.; degenerates, 1.6 per cent. Many macrocytes, microcytes, poikilocytes and oval cells. No nucleated forms seen.

Urinary Findings: 24 hour specimen, 1025 c.c.; specific gravity, 1.017. Acid. Color pale yellow. Tests for albumin and sugar negative. The small sediment contained a few leucocytes, epithelial cells, and a few round granule cells. No casts.

Fecal Findings: The stools were small, thin and watery, brown, containing mucus in small flakes. No occult blood. Microscopically a few undigested meat fibers and starch were seen. No cells and no parasites found.

Test Meals: These showed an absence of hydrochloric acid. Total acidity low. Rapid motility. Low peptic digestion. No lactic acid. Microscopically a few short motile rods with curved ends.

Treatment.—The patient was put on "anemic diet," consisting of eggs, raw beef and two-hour liquid feeding. He was

1. Cunningham (John H.): Ann. of Surg., February, 1907.