Chittenden (R. H.)

DIGESTIVE FERMENTS.

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This pamphlet covers the following recent literature upon the subject of Digestive Ferments;

Chittenden (R. H.)

[FROM THE PHILADELPHIA MEDICAL NEWS, FEBRUARY 16, 1889.]

Observations on the Digestive Ferments.

READ BEFORE THE SECTION ON PÆDIATRICS OF THE NEW YORK ACADEMY OF MEDICINE, JANUARY 23, 1889.

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Recent years have witnessed a marked development in our knowledge of the physiology of digestion. A great mass of histological and physiological details has been gradually accumulated by which a clearer insight has been obtained into many of the processes of secretion, digestion and absorption. Chemical science has lent its aid and given us light on the composition and character of the digestive juices, and on many hitherto obscure points in the metamorphism of the various food stuffs, and at the same time taught us to appreciate its value in the study of scientific medicine.

There is, I think, no branch of medicine where a proper appreciation and true understanding of physiological processes is so necessary as in the pathology of digestion. In the words of Dr. Ewald, "digestion is comparable to a complicated clock-work, the derangements of which are readily shown by the movements of the hands, but the causes of which are difficult to discover from the complexity and concealed position of the movement. Therefore, the pathology of digestion requires a well grounded knowledge of the complex processes which affect the transformation of our food into chyle."

Among the more recently acquired facts pertaining to digestion none are of more importance than those which relate to the digestive ferments. In the processes going on in the alimentary canal, by which the nutritive portions of the food are transformed into soluble and diffusible products fitted for the nourishment of the blood and of the tissues, ferments play an all-important part; without the action of the unorganized ferments, the nutrition and life of the organism would be impossible. As you well know, the more important digestive ferments or enzymes are of two kinds, the amylolytic, acting on starchy matter and the proteolytic, acting on the albuminous food stuffs. As examples of the former we have the ptyalin of saliva and the amylopsin of pancreatic juice, as well as the diastatic ferment of the bile; as examples of the latter, the pepsin of the gastric juice and the trypsin of the pancreatic fluid.

The terms fermentation and ferment may be variously defined, but yet after all we cannot add much to the definition current in the fourteenth century, viz.: "A force, which, without becoming weaker itself, can produce great effects in other masses." We know that this is not strictly correct, yet the amount of ferment involved in any given fermentation is, as a rule, so infinitesimally small, so out of proportion to the magnitude of the chemical processes or changes caused by it, and at the same time so continuous in its action, that we may well marvel at its power and wonder at its methods. We feign knowledge, however, and call it a *catalytic* action, a term which clearly exposes our ignorance, but which helps to foster our self-esteem.

The amylolytic and proteolytic ferments are alike in that they act only in the presence of water; that the products of their action contain, as a rule, more oxygen and hydrogen than the original matter, thus implying a hydration process; and that their action is most energetic at the temperature of body. They differ, however, in the medium in which they act; the amylolytic ferments being most energetic in a neutral fluid, wholly inactive in the presence of free acids; the proteolytic ferment pepsin, on the other hand, acting only when in combination with an acid, preferably hydrochloric, while trypsin acts best in an alkaline medium, although also active in a neutral fluid. These, what may be called minor points of difference, are essential ones, however, and serve important purposes in the economy. For the ferments are extremely sensitive to the action of foreign matters and the simple changes of reaction from acid to alkaline and vice versa met with in the alimentary tract are sufficient to destroy the different ferments as they are exposed to the changed conditions in their journey onward and doubtless only such escape destruction as are absorbed and ultimately excreted through the kidneys. Thus, as we shall see, the amylolytic ferment secreted by the salivary glands is undoubtedly destroyed by the acid of the gastric juice, the proteolytic and rennet ferments, secreted by the gastric glands are destroyed by the conjoined action of trypsin and the alkaline salts of the pancreatic and intestinal secretions, while the ferments of the pancreatic juice are probably in turn destroyed, at least in great part, by the acids of the large intestines.

Bearing in mind the extreme importance to the economy of these unorganized ferments, it may not be amiss to consider briefly some of the conditions which modify their activity. I am aware, however, that I am dealing with a much abused subject, one possibly worn threadbare, certainly one, concerning which, of late years, much has been said and written. But there are many conflicting statements, many downright contradictions, and I have ventured out of my experience in the laboratory to present to you the results of my own observations, enlarged somewhat by those of others which have seemed to me worthy of credence. A somewhat continuous study of the digestive ferments in their relation to normal digestive action has led to an accumulation of data (See Studies from the Laboratory of Physiological Chemistry. Sheffield Scientific School of Yale University, Vols. I-III), most of which, to be sure, has come from bottle and test-tube study, but yet I think is not to be ignored on that ground, nor on the other hand to be accepted necessarily in its entirety, but to be looked upon as a statement of fact so far as it goes, and as a suggestion to be tested clinically when of sufficient importance. So far as the pure chemistry of digestion is concerned, the nature of the ferments and their action, the influence of various agents on their activity etc., the laboratory is the proper place for such study and the data so obtained may be of great advantage in pointing the way for clinical experiments. It is to be ever borne in mind, however, that the living alimentary tract is a somewhat different mechanism from a glass beaker, and that in the former we have to deal with a complication of conditions not met with in our artificial digestions.

In considering first the action of the amylolytic ferments, we will speak only of the ptyalin of saliva and the diastase of malt, the one as an illustration of a normal digestive ferment, the other as a good example of a common remedial agent.

What is true, however, of the ptyalin of saliva is also applicable to the amylolytic ferment of the pancreatic fluid.

Human mixed saliva as ordinarily secreted has an alkaline reaction, the average of 51 samples showing an alkalinity equal to 0.08 per cent. sodium carbonate. The highest amount found was 0.144 per cent. the lowest 0.059 per cent. In spite of this being the normal reaction of the secretion, its power of digesting starch is far greater when the fluid is exactly neutral than when alkaline, a difference which shows still more distinctly the greater the fluid is diluted. The ferment acts most energetically in a neutral fluid. The same is true of the diastase of malt, its diastatic action showing stronger in a neutral fluid than in an

alkaline medium. Increasing the alkalinity of the fluid, either diastase or saliva, tends to retard the amylolytic action of the ferment, the extent of retardation being in proportion to the amount of alkali carbonate present. The percentage of alkali, however, which hinders diastatic action can be designated only for definite mixtures, being dependent upon the dilution of the fluid, and consequently upon the amount of albuminous matters and inorganic salts present.

The presence of 0.3—0.5 per cent. sodium carbonate will almost entirely stop the action of undiluted saliva on starch, while with neutral saliva greatly diluted, the presence of even 0.005 per cent. sodium carbonate will diminish decidedly the action of the ferment. Dilute alkalies not only hinder the action of these amylolytic ferments, but they also destroy them, especially at the body temperature. Their destructive power, however, is not as great as their retarding action. While these facts plainly indicate the extreme sensitiveness of the ferments towards alkaline fluids, we must not be too hasty in assuming a destructive action whenever alkalinity becomes pronounced. Peptones and proteid matters in general all tend to diminish and even prevent in part the retarding and destructive action of dilute alkalies, hence in the intestinal canal and elsewhere where the products of proteolytic action or other forms of proteid matter are present, the amylolytic ferments may endure the presence of amounts of alkalies which alone would quickly lead to their destruction.

Towards acids, the amylolytic ferments, both ptyalin and diastase are more sensitive even than towards alkalies. When diluted neutral saliva, or a solution of diastase, is mixed with diluted hydrochloric acid in such proportion that the mixture contains only 0.003 per cent. of the free mineral acid, amylolytic action is stopped almost completely. With 0.005 per cent. of free hydro-chloric acid,, destruction of the ferment is complete in a very short time, especially at the body temperature.

It has been generally held hitherto, and is even now to some extent, that the ferment of saliva and diastase as well, regain their power of transforming starch into sugar when they reach the small intestines, where the contents are alkaline, this view assuming that in the stomach the activity of these ferments is simply suspended by the acidity of the gastric juice. It has even been questioned whether the acidity of the stomach contents ever becomes sufficiently great to completely stop the solvent action of the amylolytic ferments on starch. Many eminent authorities stand committed to this view of non-destruction by the gastric juice, but it is a question easily settled by experiment and I am quite convinced that the presence of a few thousandths of one per cent. of *free* hydrochloric acid is sufficient to quickly stop all amylolytic action. We are to bear in mind, however, that because a fluid reacts acid, to test papers, it does not necessarily follow that it contains free acid. In gastric juice for example, especially after digestion is well under way, there are present comparatively large amounts of albuminoses, peptones, etc., all of which unite with the acid of the gastric juice, forming a *loose* chemical combination to be sure, but yet one in which the acid is far less powerful towards ferments at least, then when uncombined. Hence the question of retardation and destruction of amylolytic ferments in the stomach needs further consideration; we need to know how the proteid matter affects the action of the acid of the gastric juice and we find by experiment that nearly all forms of albuminous matter prevent to a certain extent the destructive action of the acid. The acid-proteids formed, however, have more or less of a destructive action themselves and when all the proteid matter present in a given mixture is completely saturated with acid, although no free acid may be present, the amylolytic ferments soon lose their action on starch, and in a short time are completely destroyed. Hence, it follows, that while the proteids of the food probably protect for a time the ptyalin of the saliva, or other amylolytic ferments introduced, by combining with the hydrochloric acid as it is secreted, in a very short time these must become saturated and free acid be

present, and as soon as free hydrochloric acid is present, or even before, a rapid destruction of the amylolytic ferments must take place. And to this destructive action must be added also the slower action of the acid-proteids. That free acid is normally present in the stomach contents can be easily shown by several tests, notably with tropæolin oo. The length of time after the ingestion of food, before free acid makes its appearance in the stomach, must be variable, dependent in great part upon the amount and character of the food taken. There is, I think, among many physiologists a growing impression that for 15 to 30 minutes after taking food an active digestion of starch goes on in the stomach. Von Velden* found, by methods perhaps somewhat questionable, that for a time varying from three-quarters to two hours after eating, the fluid in the stomach, obtained by a stomach pump, gave no color reaction with methyl aniline violet or tropæolin for free acid, although the mixture showed an acid reaction to test papers. Uffelman† likewise found a similar absence of free hydrochloric acid in the case of a boy with a gastric fistula and fed on a mixed diet, free acid appearing from forty-five to sixty minutes after the ingestion of food Kretschy and Seemann obtained similar results. More recent experiments of Ewald,‡ however, appear to show that the time of appearance of free acid depends entirely on the food; thus, in one experiment, with a person where vomiting could be produced at will, a meal of 60 grams of wheat bread was followed by the appearance of free hydrochloric acid in the stomach contents in thirty minutes; with hard boiled eggs even after fifteen minutes. With a moderate meat diet (120 grams) free hydrochloric acid was detected only after 1½ hours. Further, Ewald and Boas§ by experiments on inmates of the "Stœdtische Frauen-Siechen-Anstalt," Berlin, have found that on feeding starch paste (200-300 c.c.) made from either potato or wheat starch, free hydrochloric acid appears in the stomach contents very quickly. The experiments were conducted on patients with sound stomachs, the stomach being empty and indeed rinsed out with water just prior to the experiment and the wash-water proved free from acid. In this way they found that the ingestion of the starch paste was followed in one case by the appearance of free hydrochloric acid in ten minutes, the fluid vomited containing 0.04 per cent. HCl, the acid increasing after 27 minutes to 0.28 per cent. HCl. In another experiment after the same order 0.13 per cent. HCl was found in the fluid ejected after fifteen minutes, while at the end of thirty minutes the acid had increased to 0.29 per cent. In no case was lactic acid found in the ejected matter.

These same investigators have also in part confirmed our statements regarding the action of acids on the amylolytic ferment of saliva by a series of interesting chemical experiments on patients in the Frauen-Siechen-Anstalt. By feeding a one per cent. starch paste solution, to which a definite amount of hydrochloric or other acid had been added, to patients whose stomachs had been previously rinsed with water, they found that the smallest percentage of hydrochloric acid which would hinder the formation of reducing substances was 0.066 per cent. the stomach contents being ejected or withdrawn 5 to 45 minutes after the ingestion of the starch. With some patients, however, the acid could be raised to 0.1 or even to 0.12 per cent., and still have a trace of reducing bodies found, the latter being presumably sugar. With lactic acid, the amount could be raised to between 0.1 and 0.2 per cent., and still have some starch converted. With butyric acid 0.2 per cent., allowed some conversion. It must be remembered, however, that these percentages are simply the percentages of acid in the starch mixture, introduced into the stomach, and not the percentage of acid in the stomach contents, where there would naturally

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*Zeitschrift für physiologische Chemie, 3, p. 205.
†Jahresbericht der Thierchemie, 1880, p. 302.
‡Virchow's Archives, Vol. 101, p. 362.
§Virchow's Archives, Vol. 104, p. 272.

occur a dilution and partial neutralization from the inflow of alkaline saliva, counterbalanced perhaps by the secretion of acid gastric juice. The most important point in this connection, however, is the fact that such conversion of starch as does occur in the stomach under these circumstances takes place during the first five minutes, the amount of sugar found in the ejected fluid being the same at the end of five minutes as at twenty minutes; further, the amount formed is quite small, implying that the ferment is quickly stopped in its action by the acid present. Ewald also concludes that the presence of 0.077 per cent. of hydrochloric acid is sufficient under the above circumstances to completely destroy the ferment. Coupling these facts with those already mentioned, I think we can safely conclude that the action of the diastatic ferments can at the best continue only for a short time in the stomach, and that cessation of amylolytic action is quickly followed by destruction of the ferment, through the action of the free and combined hydrochloric acid.

Further, it is obvious that the administration of diastatic ferments, however active, by the mouth, with the intention of supplementing the pancreative digestion of starch in the small intestines, can be of little value since the ferment must inevitably be destroyed before reaching the seat of action.

The extreme sensitiveness of the amylolytic ferments towards acids is substantiated by their behavior towards many common therapeutic agents; for the quantitative data, showing the exact amount of retardation or stimulation of amylolytic action, see Vol. I of Studies in Physiological Chemistry, Yale University. Many of the so-called antiseptics and germicides likewise show marked action on these ferments even when present in very small quantities. Mercuric chloride or corrosive sublimate, also mercuric iodide and bromide retard the action of the amylolytic ferments, even when present in a few thousandths of one per cent. Curiously enough, mercuric cyanide, when present in small amounts, appears to increase the solvent action of these ferments on starch. Large percentages, however, retard their action. Sulphate of copper has a very marked inhibitory action, while lead acetate has a retarding action only when present to the extent of two or three per cent. Arsenious oxide and ammonium arseniate in small fractions of a per cent., both cause neutral saliva to convert a larger amount of starch into sugar than the saliva alone would do, while arsenic acid retards the action of the ferment. Tartar emetic in small amounts has a marked stimulating influence on the salivary ferment, but large amounts, as 5 per cent., very noticeably diminish the amount of sugar formed. Potassium chlorate in small quantities increases the amylolytic action of saliva, while the presence of even 5 per cent. of the salt has only a slight retarding effect. Sodium chloride likewise has a slight stimulating action and large percentages cause only a slight diminution in the amount of starch dissolved. Many of the alkaloidal salts cause the salivary ferment to form an increased amount of sugar, apparently through stimulation of the ferment, notably morphine sulphate, quinine sulphate, cinchonine, and cinchonidine sulphates, atropine sulphate and brucine sulphate. Strychnine sulphate, on the other hand, has a slight retarding action on the ferment. Antipyrin and antifebrin both have a slight inhibitory action on the salivary ptyalin. Urethan, in small fractions of a per cent. has a slight stimulating action, while larger amounts diminish somewhat the quantity of sugar formed. Thallin sulphate in very small percentages has a noticeable stimulating action, while paraldehyde has a marked inhibitory effect.

Of gases, oxygen and carbonic acid both decidedly increase the amount of sugar formed by neutral saliva, while hydrogen noticeably diminishes the action of the ferment.

Pepsin, the best known of the proteolytic ferments, and perhaps the most important, has been the subject of study for many years. Ever since Eberle in 1834 called attention to the solvent power of an acid extract of the stomach mucosa, investigators have been at work in a vain attempt to isolate the active principle in a pure state. Schwan named the hypothetical substance, pepsin, and Wasmann just fifty years ago made an elaborate but fruitless attempt to isolate the pure ferment. Even at that time the power-

ful digestive properties of the ferment were recognized, for, Wasmann states that a weak acid solution containing only $\frac{1}{60000}$th part of the impure ferment will dissolve coagulated albumen in from six to eight hours. A long row of illustrious names may be added to the list of those who have endeavored to widen our knowledge of this proteolytic ferment; Pappenheim, Valentin, Elsässer, Frerichs, C. Schmidt, and many others may be mentioned as among the first to work upon this subject, while nearly every prominent physiologist since has made some contribution to broaden our knowledge of this digestive ferment.

Among the many facts connected with the proteolytic action of pepsin which it is important for us to remember is that the acidity of the gastric juice is mainly due to free hydrochloric acid. The elaborate experiments of Bidder and Schmidt still stand the test of criticism and while we have many times, especially in disordered conditions of the stomach, lactic, butyric, acetic and possibly other acids present in the stomach contents, we are to look upon them as the products of various forms of fermentation, rather than as secretory products from the stomach cells.

Richet (Du suc gastrique chez l'homme et les animaux) has claimed that the hydrochloric acid of the gastric juice does not exist free, but in a state of loose combination with leucin, as chloride of leucin. His experiments are of value, since they furnish added proof that the gastric juice contains but one mineral acid, but few physiologists are inclined to believe that it exists combined with leucin. Certainly for a vigorous gastric digestion, free acid is as indispensable as pepsin itself. Leucin is undoubtedly often present in natural gastric juice and in extracts from the stomach mucosa, but I have many times also found considerable quantities of xanthin, hypoxanthin and other similar crystalline extractives, and I see no reason for assuming a combination in the one case any more than in the other. As to the strength of hydrochloric acid in the gastric juice, Richet, as the mean of seventy observations on a patient who had had gastrotomy performed for an impermeable stricture of the œsophagus, found 1.3-1.7 per mille. Other physiologists give somewhat higher results and 0.2 per cent. is usually taken as the average content of acid in active gastric juice. It can be easily shown, however, by experiment that the strength of acid best fitted for digestion depends somewhat upon the amount of ferment present and the character of the proteid to be digested. Using a pepsin extract of moderate strength and blood-fibrin as the proteid to be digested, we have found by quantitative trials that the most vigorous proteolytic action is usually obtained in the presence of 0.1 per cent. pure HCl. Thus in one series of experiments where the amount of pepsin was the same throughout with 0.05 per cent. HCl 73.8 per cent. of the fibrin was dissolved; with 0.1 per cent., HCl 89.3 per cent. of the fibrin; with 0.2 per cent. HCl 84 per cent. of the fibrin; with 0.3 per cent. acid, 81.7 per cent.; while with 0.4 per cent. HCl only 63.8 per cent. of the fibrin was dissolved. It is also to be remembered that while the proteolytic action of the ferment is most vigorous in the presence of hydrochloric acid, other acids will to a greater or less extent take its place, viz., phosphoric, nitric, sulphuric, oxalic, acetic, lactic, etc. Thus with oxalic acid, proteolytic action is vigorous in the presence of 0.5-2.0 per cent. of the acid, most vigorous with 1.5 per cent. such a mixture dissolving about three-fourths as much proteid as the same amount of pepsin with 0.1 per cent. hydrochloric acid.

With nitric acid, proteolytic action is most energetic in the presence of 0.2 per cent.; with sulphuric acid in the presence of 0.3 per cent. Compared with 0.1 per cent. hydrochloric acid, nitric acid is more than four-fifths as active, while sulphuric acid is little more than one-fourth as active and acetic acid is practically worthless. Hydrobromic and hydriodic acids can, to a certain extent, replace the hydrochloric acid of the gastric juice as Putzeys (Jahresbericht der Thierchemie, 1877, p. 279), has previously found, although they are both much less active than the latter. Moreover, hydrobromic acid is much more efficient than hydriodic acid in connection with the ferment, for in comparatively large doses the latter will completely stop all proteolytic action.

Whenever bromides and iodides are taken into the stomach they are supposed to be decomposed by the acid of the gastric juice with formation of hydrobromic and hydriodic acids respectively, by which the retarding action of these two salts on gastric digestion is produced. Hence, as a practical result the bromides and iodides should be given ½ to 1 hour before meals.

There are, I presume, many diseased conditions where imperfect digestion is due as much to the want of the necessary acid as to lack of ferment. Thus in fevers, as a rule, from whatever cause, a less active gastric juice is secreted than normal, one possessed of far less proteolytic action, though generally acid. The acidity, however, is frequently diminished and, as Ewald remarks, confirms the old habit of prescribing phosphoric or hydrochloric acid in fever mixtures. The simple fact that the stomach contents are acid does not necessarily indicate that the fluid is of the proper degree of acidity or even contains the proper acid, suited to the ferment. Acetic, lactic or butyric acid may be present and render the stomach juices decidedly acid and yet it may be necessary to give acid, in order to bring the acidity up to the point suitable for the best action of the pepsin. It is also possible to give an acid, as possibly salicylic, which will have a double action; viz., an antifermentative one and a digestion-promoting one. Certainly in many forms of dyspepsia, as the researches of Ewald have shown, the derangement originates in the absence of the required degree of acidity rather than in insufficiency of pepsin. In many such cases there may be an "acid stomach" and yet the secretion of normal gastric juice be practically suppressed, the acidity being due mainly to lactic acid doubtless formed by fermentation in the stomach; an acid which acts with pepsin only about ⅛ or ⅓ as well as hydrochloric acid. Occasionally, as you know, the stomach contents have an alkaline reaction, as when a strongly alkaline transudation is poured into the stomach in connection with diminished or entirely abolished secretion of acid. Again, there are many other forms of dyspepsia or gastric troubles where there is a relative insufficiency of secretion, where pepsin as well as acid is wanting and where artificial digestive preparations are especially called for.

With reference to the influence of drugs on the proteolytic action of pepsin-hydrochloric acid we have considerable definite information, partly as the result of experiments with artificial gastric juice and partly from observation on patients and animals with gastric fistula. Nearly all metallic salts diminish the proteolytic action of the ferment quite decidedly, even a few hundredths of a per cent., as a rule, producing a noticeable effect. Thus cupric sulphate, lead acetate, mercuric chloride or corrosive sublimate, mercuric bromide, iodide and cyanide, salts of tin, zinc, manganese and iron, all have more or less of a retarding action on the digestive power of pepsin. Iron salts retard the action of the ferment much more than the corresponding salts of manganese. Mercurous chloride or calomel has been shown by Wassilieff to have no action whatever on the ferment. The action of these metallic salts is due, as a rule, to the combination of the metal with the proteid to be digested, forming an indigestible compound, and in part to a direct action on the ferment itself. We have determined with all of these salts the exact amount of retardation or stimulation of peptic action under definite conditions, but I refrain from troubling you with the figures, especially as I think that the *extent* of action of a given amount of any drug in the stomach is, as a rule, greatly dependent upon the conditions, which are naturally variable, especially the strength of the pepsin-acid solution, the amount and character of the proteid to be digested, etc., and that it is better in applying these results to content ourselves with statements regarding the general nature of the action. Arsenious acid has a noticeable stimulating or accelerating action on the ferment, the presence of even 0.5 per cent. of this substance causing the pepsin mixture to dissolve a much larger amount of albumen than the pepsin-acid alone will do. Arsenic acid has the same action, only still more pronounced, and the presence of even 2 per cent. of this compound leads to increased proteolytic action. This certainly accords with the generally accepted views as to the influence of arsenic on nutrition in general.

Potassium permanganate as a very energetic action on pepsin, the presence of even 0.005 per cent. in a digestive mixture reducing the action of the ferment to one-quarter its normal. Potassium cyanide and ferrocyanide have marked inhibitory action on the ferment. Potassium chlorate and nitrate likewise retard the action of pepsin, and when present to the extent of 1.5 per cent. both salts reduce the proteolytic action to one-quarter that of the normal ferment. Sodium tetraborate or borax and the chlorides of sodium, potassium and ammonium, all retard the digestive power of the ferment. Sodium chloride in small amount, however, has a noticeable accelerating action. Potash and ammonia alum both retard digestive action. Sulphates of magnesia and soda likewise retard the action of pepsin, even 0.005 per cent., having a noticeable effect

Nearly all the alkaloidal salts have more or less of a retarding action on pepsin; thus strychnine, brucine, veratrine, morphine, narcotine, quinine, cinchonine and atropine sulphates all reduce the action of the ferment, morphine sulphate less than the others.

Bearing in mind that pepsin acts far less energetically with sulphuric and acetic acids than with nitric acid and with the latter less actively than with hydrochloric, we can easily see that, as a rule, everything else being equal, sulphates will retard the digestive action of pepsin more than nitrates, and the latter more than chlorides, and if we are to apply such results as these to our practice it would be to use chlorides of the alkaloids, where practicable, rather than sulphates, and the same of inorganic salts. To be sure, after a short time the alkaloid or its salt will have passed into the circulation and the stomach be freed from its influence, but it is well to heed the small things as well as the great, and if we can accomplish the same physiological effect with a chloride as with any other salt and thus avoid or lessen possible disturbance in the stomach it is perhaps as well to do so.

With alcohol we have a double effect to consider; the results of many experiments have shown plainly that the presence of alcohol impedes the proteolytic action of pepsin, even though it is present in comparatively small quantity, but as Gluzinski (Jahresbericht der Thierchemie, 1886, p. 263) has shown, alcohol rapidly disappears from the stomach, even 100 c. c. of 25 per cent. alcohol disappearing inside of 15 minutes. While in the stomach, alcohol undoubtedly retards the solution of proteid matter. Shütz finds that 2 per cent. has a retarding action, while 10 per cent. causes a very great retardation and 15 per cent. allows only a slight digestive action. Bikfalvi finds similar results as do likewise Ogata and Klikowicz. The disappearance of the alcohol, however, is followed by the secretion of an active, strongly acid gastric juice, which continues generally long after the food is entirely digested. Hence, under the influence of alcohol there is often an accumulation of large quantities of fluid in the stomach, frequently colored yellow by bile. With small quantities of alcohol, therefore, especially with an abundance of food, there is an undoubted stimulation of proteolytic action induced mainly, if not wholly, by the increased secretion of hydrochloric acid. Under such circumstances the first stage of retardation is hardly to be considered, since the alcohol disappears so rapidly. With large amounts of alcohol, the mechanical functions of the stomach are interfered with, and thus the food compelled to remain a much longer time in the stomach than normally.

Beer, wine and stronger spirits all have retarding action according to the experiments of Ogata (Archiv. f. Hygiene 3, p. 204) on a dog with gastric fistula. In the case of beer, Ogata found that the retarding action was due equally to the alcohol contained in it and to the extracted matters. Even sugar, both grape sugar and cane sugar, when taken in quantities above 10 grams, tend to retard the digestive action of pepsin, but on account of their rapid absorption such action is of course only temporary. Soda-water or carbonic acid water in quantities of 200 c. c. or more, moderately strong infusions of tea and coffee and 200 or 300 c. c. of spring water were all found to have no appreciable influence on gastric digestion in the stomach itself.

Sodium salicylate (Klikowicz, Jahresbericht der Thierchemie, 1885, p. 277) in doses of

from 2.5 to 5 grams has a marked retarding influence on the digestive action of pepsin. Chloral hydrate, according to Klikowicz, is without action on pepsin in doses up to 1 gram. With 2-3 grams, however, there is noticeable retardation of digestive action, which with larger doses becomes still more pronounced.

Among the newer drugs, antipyrin and antifebrin, both retard the action of pepsin; antipyrin, when present to the extent of 3 per cent., almost entirely stopping the action of the ferment. Paraldehyde has a very pronounced stimulating effect when present in small quantities, and even 2 per cent. has only a slight retarding effect. Urethan has a very slight inhibitory effect, while thallin tends to increase the digestive action of pepsin.

In contact with dilute sodium carbonate, pepsin is very quickly destroyed, especially at the body temperature. Experiments made with scale pepsin and pepsin extracts from the stomachs of various animals have shown plainly that destruction invariably takes place in the presence of 0.05 per cent. of the alkali carbonate, hence when the acidity of the gastric juice is neutralized in the small intestines and the mixture becomes alkaline, there will be a rapid destruction of the pepsin, aided, as Langley has found, by the trypsin of the pancreatic fluid.

Trypsin, the proteolytic ferment of the pancreatic juice acts freely only in neutral or alkaline fluids, slowly and imperfectly in feebly acid fluids. Thus in an experiment on fibrin a neutral solution of trypsin digested 77 per cent. of the proteid, while the same amount of ferment in the presence of 0.4 per cent. sodium carbonate digested 96 per cent. in the same length of time, and in the presence of 0.1 salicylic acid only 44 per cent. of the proteid; under ordinary circumstances the ferment appears to act most energetically in the presence of 0.5 per cent. sodium carbonate, but will act even in the presence of 5 per cent. of the alkali salt. In no case will a salicylic acid solution act as vigorously as a neutral solution of the ferment. It appears, however, that in the acid-reacting fluid the ferment simply acts more slowly and if time be given, will ultimately approach the action of the neutral fluid. In such cases, however, the salicylic acid is not free, but combined with the proteid matter; free acids, either mineral or organic, even a few thousandths of a per cent. completely stop the proteolytic action of trypsin and the addition of dilute hydrochloric acid to a neutral trypsin solution will prevent all proteolytic action, even before the proteid matter is completely saturated; after which the acid quickly causes the death of the ferment. A glycerin extract of the pancreas, for example, on being warmed at the body temperature with even 0.05 per cent. hydrochloric acid soon loses its proteolytic action, and, as Langley has shown, the presence of pepsin aids in the destruction. Hence it is obvious that pancreatic extracts or ferments given by mouth can be of no value whatever, since the proteolytic ferment at least will undoubtedly be destroyed in the stomach before reaching its normal sphere of action. It seems to me very desirable, however, to be able to use the pancreatic ferments as an aid to pancreatic digestion in the small intestines. The use of such preparations, however, even though fortified by doses of sodium carbonate or bi-carbonate can avail little, since destruction must inevitably follow their entrance into the stomach. I have seen, however, proclaimed somewhere a form of capsule insoluble in dilute acid, but soluble in alkaline fluids, which if truly possessed of such properties could be made an easy means of introducing both the amylolytic and proteolytic ferments into that portion of the alimentary tract where they are capable of performing their characteristic functions. Without some such method of protection, it is of course useless to administer trypsin by mouth with any hope of gain to the economy.

As you doubtless know, the action of trypsin is peculiar in that there is no swelling of the proteid matter as in the action of pepsin and acid, but the albuminous substance is eaten into, crumbles, falls apart and then dissolves. Further, the action of trypsin is peculiar in that it not only converts the albumen into peptone, but also de-

composes a portion of the latter with formation of leucin, tyrosin, and other products. With pancreatic digestion, the digestive function of the alimentary canal reaches its highest point, and so far as proteolytic action is concerned, trypsin is undoubtedly more highly organized than its neighbor pepsin; the changes produced by it are more pronounced and deep-seated.

I would be glad to give you some idea of the relative activity of pepsin and trypsin, as proteolytic ferments, but this I can hardly do with exactness. In normal digestion the two ferments work under such divergent conditions and the products of their action are so different that it would perhaps be hardly correct to measure their relative action by the amounts of albumen they are capable of dissolving. Again, so far as I am aware, attempts to obtain the pure ferments for pharmaceutical purposes have not as yet been as successful with trypsin as with pepsin. Looked at from the purely physiological standpoint, I am of the opinion from my own experiments with the two ferments, that pure trypsin will prove to be more energetic in its action than pepsin, but the manufacturing chemists have yet to make a trypsin preparation equal in action to many of the brands of pepsin now in the market.

As a solvent of pseudo-membranes, as in diphtheria and in croup, the digestive ferments are certainly destined to prove of considerable value. Both pepsin and trypsin are recommended, but from a partial study of the various digestive ferments at present obtainable, I am inclined to consider pepsin as the more efficacious. If a trypsin preparation could be obtained in strength equal to many of the preparations of pepsin I should be inclined to its use, for the reason that it acts best in an alkaline medium, that it will eat into and disintegrate the fibrinous membrane, rather than first cause it to swell up, that the alkaline secretions of the buccal and other glands will favor its action, that the alkaline fluids possible to introduce with the trypsin may have a slight solvent action in themselves on the diphtheritic membrane, and that the ferment will act after the excess of alkaline carbonate has disappeared.

These minor advantages, however, are, at present at least, far more than counterbalanced by the much greater activity of the ordinary pepsin preparations. Further, a large number of experiments to demonstrate the influence of various therapeutic agents on the proteolytic action of trypsin have shown me that as a rule this ferment is far more sensitive to the presence of foreign salts and drugs than pepsin is, and while this fact need not be considered here, yet it may influence us somewhat in favor of the latter ferment. Trypsin, however, is not much affected by the powerful oxidizing salt potassium chlorate, the presence of even 5 per cent. of this salt causing only a slight diminution in the solvent power of the ferment.

As we have seen, the solvent action of pepsin on proteid matter is most pronounced in the presence of 0.1-0.2 per cent. hydrochloric acid, but a thin solution of pepsin with this acid would very quickly rinse down when sprayed into the throat, for the dissolving of pseudo-membranes. Admixture of glycerin will in part prevent this and keep the ferment for a longer time in contact with the surfaces to be dissolved. Obviously, the operation of painting or spraying must be frequently repeated in order to keep the surface well moistened with the digestive fluid. Again, since pepsin will not act at all in a neutral or alkaline fluid, it is plainly better to have the digestive mixture at the outset contain at least 0.3-0.4 per cent. actual hydrochloric acid. This will in part provide somewhat for the natural dilution of the acid and also for the neutralizing action of the saliva and other fluids. Further, acid of this dilution is innocuous and is a not unpleasant and cleansing mouth-wash. So long as the fibrinous tissue can be kept acid the solvent power of the ferment will be exerted, and in this connection it is to be remembered that there exists a mutual attraction between the acid and the proteid matter of the membrane by which the acid will be retained longer than by perfectly inert matter. It is to be remembered, however, that such dilute acid has a ten-

dency to swell up proteid matter and we can conceive of cases where such application might be deemed inexpedient. The capability of pepsin for dissolving blood fibrin is very great, and at the body temperature its action is quite rapid, and hence one would expect that under suitable conditions the fibrinous portion of a diphtheritic membrane would be attacked with considerable rapidity.

The ferment solution, however, should, be carefully brought to the body temperature prior to its introduction and the ferment itself should be of the strongest kind, so as to favor immediate action. The widespread use of pepsin for this and other purposes has led to the manufacture of large numbers of preparations of this ferment, some of which at least are of doubtful quality. This fact has been impressed upon me many times in the laboratory, where for various physiological purposes commercial pepsin has been employed. Further, during the last six months I have made a comparative study of a number of the more prominent pepsins in the market, determining quantitatively their relative proteolytic action. The general use of pepsin as a remedial agent in gastric troubles may well make us solicitous as to the character and strength of the preparation at our disposal, but as a solvent for pseudo-membranes, where rapidity of action is of the utmost importance and the life of the patient hinges on the result we should be doubly sure of the character of the ferment employed. The methods at present suggested by the different pharmacopœias for testing the digestive strength of pepsins or pepsin solutions are somewhat variable, both in respect to the strength of acid employed and in the character and condition of the proteid matter to be dissolved, and it may also be questioned whether the standard adopted is sufficiently high.

Nearly all of the methods now in vogue, either for pharmaceutical or physiological purposes, are based upon the older methods of Bidder and Schmidt, Ebstein and Greutzner Gruenhagen (Lee Herman's, Handbuch der Physiologie Band 5, 2ter Theil., p. 75–77), and shorn of their details consist essentially in a determination of the amount of coagulated egg-albumen or blood fibrin, which can be dissolved by the ferment in a given time, an excess of proteid matter being present, and the amount of albumen dissolved being taken as a measure of the proteolytic action.

Such a method does indeed show which mixture or pepsin has the stronger digestive action but does not give a very correct idea of the *relative* proteolytic power, for while the conditions in such an experiment or series of experiments appear to be the same in each case, they are in reality often very unlike. For as Thompson (The Druggist's Bulletin, Vol. 2, page, 261,) in a recent article on "comparative pepsin testing" has well said, the amount of albumen in each test may be the same and also the volume of the fluid and the amount of apparent ferment, and yet as soon as the digestion commences the weaker pepsins quickly have more surface of albumen or fibrin to work upon than the stronger and therefore show better than they should. Again all who are familiar with pepsin testing can easily see that the condition of the proteid matter to be acted upon becomes a very important factor in such a test whether blood fibrin or hard boiled egg, the fineness of its division, the completeness of its coagulation, the thoroughness with which it is kept suspended in the digestive fluid, all tend to exercise a very important influence on the final result and are necessarily a source of frequent error.

Still again, the strength of acid recommended by several of the pharmacopœias is such as to be at least suggestive of the formation of considerable acid albumen, by which the apparent strength of the ferment is correspondingly increased. To obviate these difficulties and, if possible, to insure more accurate results in pepsin testing, I have devised the following method, based upon the fact that fluid egg albumen is essentially of the same degree of digestibility as coagulated albumen (Wawrinski. Hermann's Handbuch der Physiologie, Band V., 2ter Theil, p. 83), and that the ability to form albumose and peptone is

possibly a more accurate measure of proteolytic action than the power of simply dissolving coagulated proteids.

The albumen solution is prepared after the manner recommended by Schutz (Zeitschrift für Physiologische Chemie, Band IX, p. 581). A quantity of the undiluted white of egg is freed from globulin by the addition of hydrochloric acid of specific gravity 1.12, 4.2 c. c. to 300 c. c. of albumen, shaken gently, and after standing some hours filtered. The fluid will then be found to have lost its viscosity and to be perfectly clear. The acid will likewise have neutralized the alkali carbonate present and converted the phosphates into acid salts. The solution, however, will not contain any free acid. 10 c. c. contain approximately one gram of dry albumen. The exact amount can be determined in a sample by coagulation. The solution can be kept for some days, and so used in a large number of experiments. The testing is conducted as follows: Ten or twenty c. c. of the albumen solution are measured out with a pipette and introduced into a suitable receptacle, a definite volume of the pepsin solution, say 50 c. c., previously prepared by dissolving a weighed amount of the pepsin (50–500 milligrams of the pepsin in 1 litre of the acid, according to its proteolytic power), in 0.2 per cent. hydrochloric is added, and enough more 0.2 per cent. acid to make the entire mixture 100 c. c. The fluids are then placed in a bath at 40° C. and allowed to remain there for five or six hours. (The conditions to be so arranged as not to have more than 50–60 per cent. of the albumen at the most converted into soluble products). No stirring is needed, no attention of any kind other than to keep the mixtures at the proper temperature, and there is no possible error from variations in the mechanical condition of the proteid. At the end of the allotted time, the mixtures are heated to boiling and the acid neutralized by addition of the equivalent amount of sodium carbonate, best in approximately one per cent. solution. The unaltered albumen as acid albumen is at once thrown down as a heavy flocculent precipitate, and while still hot it is collected at once on a dry, weighed filter, washed thoroughly with boiling water and dried at 110° C. From this is easily calculated the amount of albumen converted into soluble products under the conditions of the experiment from which in turn can be calculated the relative proteolytic action of the pepsins tested. The figures so obtained, if the conditions have been properly arranged, give a much closer approach to the true proteolytic power of a ferment that any similar method with solid proteids, but even this does not tell the whole truth. There is still felt the influence already mentioned of the relative excess of unchanged albumen in those digestions where the ferment action is weakest and hence after having used the above method as a preliminary test it is necessary to have recourse to a modification of the principle made use of by Brucke (Vorlesungen über Physiologie, p. 303), years ago, and recently recommended by Thompson, of using sufficient of each pepsin or pepsin solution to convert the *same percentage* of albumen into soluble products. In this way only, so far as I am aware, can the true proteolytic power of pepsin or pepsin extract be determined.

After these methods I have tested the following brands of pepsin, obtaining as a preliminary result the following figures expressive of their relative proteolytic action.

The "Pepsinum Purum in Lamellis" having the highest digestive power is taken as the standard (100):

	Preliminary test of Relative Proteolytic action.
1. Parke, Davis & Co.'s Pepsinum Purum in Lamellis	100
2. Fairchilds' Pepsin in Scale	73
3. Scheffers' dry Pepsin concentrated	70
4. Jensen's Crystal Pepsin	56
5. Ford's Pepsin in Scales	54
North's Pure Pepsin	36
Boudault's Pepsin	35
8. Royal Chem. Co.'s Pure Pepsin	27
9. Scheffer's Saccharated Pepsin	16
10. E. Merck's Pepsin Germ. Pur. Pulv	11
11. Lehn & Fink's Powdered Pure Pepsin	0

From these data, which are the average of many results, we might infer that Fairchild's pepsin, for example, contains three-fourths as much active ferment as the Pepsinum Purum of Parke, Davis & Co. and that Ford's and Jensen's pepsin contain approximately half as much true ferment as the Pepsinum Purum. Such a conclusion, however, would be fallacious and to obtain the true measure of proteolytic action we must proceed further and determine next the relative amounts of the different preparations needed to produce a like result in each case. After this method we find, for example, that it requires about twice as much of Fairchild's and Scheffer's Pepsin to form a given percentage of peptone as of the Pepsinum Purum, and that of Ford's and Jensen's preparations about three times as much, thus showing that the true difference in proteolytic power is considerably greater than the preliminary results alone indicate. As a final result then we may consider the true proteolytic power of the above ferments compared with the one of highest digestive power to be as follows:

	Relative Proteolytic Action.
1. Parke, Davis & Co.'s Pepsinum Purum in Lamellis	100
2. Fairchild's Pepsin in Scale	52
3. Scheffer's dry Pepsin, concentrated	48
4. Jensen's Crystal Pepsin	35
5. Ford's Pepsin in Scales	32
6. North's Pure Pepsin	16
7. Boudault's Pepsin	14
8. Royal Chem. Co.'s Pure Pepsin	9

In considering these results it is to be borne in mind that the same brand of pepsin is liable to slight variations in its digestive power, doubtless dependent in part upon the condition of the membranes from which it is prepared. Thus in many instances I have found one or two of nearly the same digestive strength changing their relative positions, notably, Nos. 2 and 3 and Nos. 4 and 5.

As to the actual strength of these preparations 1 milligram of the strongest pepsin converted into soluble products 198 milligramms of the pure dry albumen, which would be practically equal to 2000 parts of fluid egg-albumen.

[FROM THE MEDICAL RECORD, DEC. 22, 1888.]

PEPSIN IN SURGERY.

H. B. DOUGLASS, M. D.

The digestive ferments have only recently attained that state of perfection which enables the physician to use them successfully in the various derangements of the digestive tract, and as a solvent by local application to the diphtheritic membrane. This last use of the ferments suggested to me their use in surgical cases, and for some months past I have been using pepsin in surgical work. Pepsin is best applied in the form known as "pepsin in scales," or as an ointment with lanolin as a base:

℞ Pepsin, gr. 5c.
Lanolin, ʒ ss.
M.

The cases cited below will illustrate some of its applications.

1. In ulcerations.

Case I.—Mrs. T—— had a varicose ulcer of the leg covered with thin adherent membrane, beneath which were weak granulations. Around the ulcer for an area of two inches was an acute eczema. The ulcer was foul smelling. Pepsin ointment with cotton dressing was applied. In five days the dressing was removed. The eczematous patch was less inflamed, the discharges not offensive, and the membrane was entirely dissolved. The granulations were healthy. Bismuth was now applied and the ulcer was soon healed.

Case II.—Mrs. M. D—— presented upon the middle of the tibial crest a varicose ulcer. The base of the ulcer was covered with a thick yellowish membrane. "Pepsin in scales" was applied to this ulcer. In one week the membrane had entirely disappeared and the ulcer was in a healthy condition.

Case III.—M. D—— has a large epitheliomatous ulcer (rose cancer) of the neck. The centre of the ulcer is sloughing rapidly. The whole surface of granulations is covered with a membrane. The secretion from the ulcer is abundant and very foul. Pepsin ointment was applied daily to ulcer. In two days the surface of granulations was free from membrane and they looked smaller and red. Wherever the ointment was applied the sloughing ceased, but, from the deeper parts of ulceration the discharge was unchanged.

2. In cicatricial contractions.

Case I.—D. H. J—— two weeks ago had a periostitis of first phalanx of middle finger with cellulitis of palm of hand. The resulting abscess was lanced in two places. When he came under my observation the suppurative process had left much inflammatory induration in the palm of the hand, extending to the second phalanx. There was a small sinus leading to bare bone on the first phalanx. The patient was unable to flex the finger because the flexor tendon was adherent to its sheath, and could not extend it on account of the cicatricial condition following the abscess. Pepsin ointment was applied to the palm, and the whole covered with a cotton dressing. In three days the sinus had closed and the cicatrix was much softer. After six days the palm was markedly less indurated, and the patient could flex the second phalanx completely. In ten days the patient was able to resume his employment as a cutter, and was fully able to hold the knife steadily in his hand.

Case II.—Mrs. M. W—— had a parotid abscess complicating pyæmia. The abscess opened spontaneously and soon healed. There resulted much induration and considerable thickened cicatricial tissue, extending from the angle of the lower jaw to the zygoma, and from the sterno-mastoid muscle to the border of the masseter muscle. This cicatricial tissue produced anchylosis of the lower jaw on the affected side, so that the patient was enabled to open her mouth enough to admit solid food. Pepsin ointment was applied twice daily. In one week there was marked improvement in opening and closing the mouth, and the tumor had nearly disappeared. In two weeks there was no trace of the swelling, and movements of the jaw were perfect.

Remarks: 1. In all ulcerations covered with a slough, or having a membranous base, pepsin is of use to digest this slough and bring about a healthy condition. 2. The efficiency of pepsin ceases when the slough has dissolved. 3. In cicatricial tissue causing anchylosis pepsin is of use by dissolving the cellular element. In this condition pepsin may act similarly to mercury and the iodides, or as a digestive.

PEPSIN AND ITS INCOMPATIBLES, WITH EXHIBITION OF TESTS.*

BY JOHN R. WINSLOW, B. A., M. D., LECTURER ON CHEMISTRY, WOMAN'S MEDICAL COLLEGE, BALTIMORE.

MR. PRESIDENT AND GENTLEMEN.—Having had my attention directed to the subject of pepsin by complaints of failure or disappointment in its action, some physicians going to such an extreme as to cast it out of their armamentarium, and having before me the statement of so eminent an authority as Prof. H. C. Wood, of Philadelphia, that "probably four-fifths of the drug used is inefficient or inert from the method either of its preparation or its administration," I was led to make certain investigations, to ascertain, if possible:

1. Are the pepsins with which we are furnished active drugs?

2. Being supplied with such a drug, cannot failure in its action be in large measure attributed to its maladministration?

The literature of the subject I have found to be brief, incomplete and scattered, and deeming it a matter of importance to every general practitioner to decide how far pepsin is reliable as a medicine, I beg your attention to the conclusions reached, not so much on account of their originality as of their practical interest.

All facts go to show that the solvent action of the gastric juice is essentially due to the presence of an enzyme or ferment, termed pepsin. This converts albuminous and albuminoid food matters into soluble and dialysable form. Since the majority of these substances belong to the class of proteids this action has been designated as proteolytic.

The products of the proteolytic action of pepsin are successively syntonin or acid albumen, intermediate products termed parapeptones and true peptones. In the stomach this peptonization is usually incomplete, and a large amount of syntonin and parapeptone is passed on into the intestines.

Pepsin is a colloidal nitrogenous body, which has been but proximately isolated and whose properties are as yet uncertain. It in many respects, however, does not correspond in its reactions to proteids.

It readily undergoes decomposition, particularly when moist, and loses its activity. This is greatest, that is, it accomplishes the maximum amount of work at about 130° F. It is completely destroyed by boiling (even by 140° F.) and is checked by cold. Pepsin acts only in the presence of an acid, being completely destroyed by an alkali. The tie between the acid of the gastric juice and its pepsin is so strong that it has been termed by some writers pepto-hydrochloric acid. A commercial pepsin should present the following physical characteristics:

1. It should be light colored and free from disagreeable odor. A marked odor indicates the presence of peptones which render the pepsin hygroscopic and hasten its decomposition.

2. It should be freely soluble in water. Insolubility shows the presence of inspissated mucus, which retards its action, aids its decomposition and detracts from its true weight.

Any good influence derived from pepsin is manifestly due to its solvent power, so that this is a measure of its value. Wishing to determine the relative strength of various commercial pepsins, I have employed the following test, which is designed to reproduce as far as possible the conditions found in the human body:

Test:—Fresh eggs are boiled 15 minutes, plunged in cold water and opened. The coagulated albumen is then freed from all yolk and superficial moisture, and pressed with a spatula through brass gauze containing thirty meshes to the linear inch. Two hundred grains are then weighed out and triturated in a mortar with distilled water containing $\frac{3}{10}$ per cent. absolute HCl. This is then placed in a tube and treated with enough of the acidulated water to make five ounces. To this mixture pepsin gr. $\frac{1}{10}$ is added, and the test tube is then immersed in a water bath and heated at a constant temperature of 104° F. until one pepsin has completely dissolved all the albumen, usually requiring about four hours. As the accumulation of peptones about the albumen hinders digestion, each tube is stirred at intervals of three to five minutes. At the end of four hours the pepsin is destroyed and further digestion stopped by boiling the mixture. To this test I have subjected the following pepsins, which are arranged in the order of their superiority.

* Read before the Clinical Society of Maryland, January 18, 1889.

(EXHIBITION OF COMPARATIVE TESTS.)

1. Parke, Davis & Co.'s.
2. Fairchild Bros. & Foster's.
3. Jensen's.
4. Boudault's.
5. Ford's.
6. Lehn & Fink's (German scale).
7. Merck's.

The pepsins used were purchased by myself in the open market, and were weighed upon the analytical balance of the Johns Hopkins University. The investigations were conducted at my residence.

The foregoing method serves to give us an idea of the relative digestive activity of the pepsins, but it is by no means an accurate test of their actual proteolytic power. It has been repeatedly proven that the action of pepsin is entirely superficial and increases proportionately to the relative amount of albumen present, whether in excess or not. Now, under the preceding conditions, all of the pepsins except the most active, have during the entire test an excess of albumen to act upon, and make a showing which is falsely good when compared with it. The only accurate method of determining the comparative preteolytic power of pepsins is to determine the maximum amount of albumen that the most active pepsin can digest under proper conditions in a given time; and using this as a standard, determine empirically the number of grains of the other pepsins required to accomplish the same amount of work under like conditions, stating the results in per cent.

With this understanding as to their inaccuracy, we may utilize the result of the preceding tests. Having determined by this means the pepsin manufactured by Messrs. Parke, Davis & Co. to be the most active upon our market, digesting 2,000 times its weight of albumen, I have employed it as the standard in the succeeding tests.

In order to demonstrate the action of drugs upon pepsin and the digestive process, I have used a standard preparation containing:

Parke, Davis & Co.'s pepsin, gr. 1-10.
Coagulated egg albumen, 200 grs.
Acid dist. water (3-10 per ct. HCl), 5 ozs.

To which the following drugs have been added and the mixture digested at a constant temperature of 104° F. for four hours. The influence they have exerted can be determined by comparison with the standard preparation.

(EXHIBITION OF INCOMPATIBLES.)

Test No. 1.—This contains gr. j. sodium carbonate. The pepsin gr. $\frac{1}{10}$ was first treated with the soda, and both were then added to a standard preparation. As you may observe, the albumen is entirely undissolved. This shows that the activity of the pepsin has been permanently destroyed by the alkaline salt, and is not regenerated by the addition of acid.

This fact is well known to many of you, but it is by no means universally borne in mind. I have recently seen large quantities of the alkaline salt ordered by prominent physicians in conjunction with pepsin, both in powder and as the glycerole.

Test No. 2 contains tr. ferri chloride ℥ v, which interferes decidedly with the process.

Test No. 3 contains a $\frac{1}{5000}$ solution of the bichloride of mercury. This in common with all decided antiseptics, exerts an inhibitory action.

It is a well known fact that large percentages of alcohol precipitate pepsin from solution and destroy its digestive power. Alcohol is contained in the ordinary beverages in the following proportions:

Mild Beer, 2 to 3 per cent.
Light Wines (Claret), 8 per cent.
Whisky Brandy and Rum, 60 to 75 per cent.

On this account wines of pepsin are unscientific preparations.

Wishing to ascertain the effect of small percentages of alcohol I have prepared:

Tests No. 4 and 5. These contain respectively 1 and 5 per cent. absolute alcohol, both of which exert a decidedly inhibitory action.

Now as these solutions contain in the one case 5 and in the other 25 minims of alcohol to the ounce, the practical conclusion is that alcohol cannot, in efficient doses, be safely prescribed with pepsin.

Test No. 6 contains bismuth subnitrate gr. v., which exerts no deleterious action whatever, the deposit in the bottle consisting of the insoluble salt itself.

Test No. 7 contains ammonio-citrate of bismuth gr. v.

In this the albumen is entirely dissolved, but the solution is milky from the precipitation of the oxychloride of bismuth by the action of HCl. on the bismuth salt. In the presence of an alkali, however, the soluble bismuth salts form a colorless solution, and on account of this desideratum nearly all elixirs of pepsins and bismuth are alkaline. This at once destroys the activity of the pepsin, as you may see in

Test No. 8, which contains ʒ j of an elixir of pepsin, bismuth and strychnine, and has no digestive value whatever.

Moreover the reactions of pepsin with organic matters are not well understood, so that it is better to avoid such elixirs.

Test No. 9, contains tannin gr. v. The tannin and pepsin were first brought into contact and then added to the standard solution.

As you see, this has an injurious effect upon the pepsin.

A practical conclusion to be drawn from this, is that wines used in connection with pepsin (wines of pepsin) should be detannated.

Test No. 10, contains quinia sulphate, gr. iii, which exerts a slight inhibitory action.

Test No. 11, contains saccharine, gr. x. This decidedly interferes with the activity of pepsin and should not be employed in connection with it.

Test No. 12, contains pulv. (Willow) charcoal, gr. x, which has no deleterious action upon digestion, the deposit in the bottle being the charcoal itself.

In order to demonstrate the results obtained by ordering "saccharated pepsin" without specification, I have purchased specimens of 4 prominent druggists.

Four grains of each have been added to a standard preparation containing 5 ounces acidulated ($\frac{3}{10}$ per cent. HCl) distilled water, 200 grs. coagulated albumen and digested at a constant temperature 104° F. for 2½ hours. The digestive activity of the same quantity of the different preparations is seen by the result to vary greatly.

The conclusions to be drawn, gentlemen are obvious:

1. There is a difference, and a marked difference, in the activity of the many varieties of this drug. And it is to our own interest to decide for ourselves and to specify the variety we will employ.

2. Having a drug so delicate in its nature, whose reactions with other substances are so intricate and ill-understood, we cannot be too particular in our method of its administration. The best results may be expected from pepsin when given alone, either in powder, or solution in glycerin, or in a freshly prepared solution in acidulated water.

While the action of pepsin seems to be catalytic and a small quantity of it should digest an almost unlimited amount of albumen, the conditions necessary for such action do not exist in the living stomach, particularly one in those conditions of disorder or disease in which this drug is indicated. We can not then rationally expect a minute quantity of the drug to efficiently digest unreasonable amounts of improperly prepared food. Not only must a drug of high digestive activity be employed, but the dose must be sufficient. Of course the more active the drug the smaller may be the amount employed.

Since the condition of the stomach most favorable to the activity of pepsin would seem to exist at that time, it is best administered during or immediately after a meal.

[FROM THE PHARMACEUTICAL RECORD, FEBRUARY 4, 1889.]

DIGESTIVE FERMENTS.

BY J. LE ROY WEBBER, PH. G.

At a meeting of the Detroit Pharmaceutical Association, held on January 2 at their rooms in the Cowie Building, in Detroit, Mich., by invitation, a lecture on the digestive ferments was delivered, of which we present the following abstract:

Every mental and physical process or effort causes a waste of bodily tissue. This waste is repaired in the conservation of living organisms by the assimilation or incorporation of matter formerly extraneous. As much needed material exists in the external world in an unassimilable form, this must first be converted. The processes of conversion known as digestion and assimilation are therefore eminently deserving of our intelligent and careful study.

Passing over, for the present, the preliminary subdivision of mastication—an important matter, however—we are met at the outset, or very entrance to the alimentary canal, by the beginning of an interesting series of changes, all essential to the existence of the individual.

In the human animal, as in many others, where the starch of the vegetable kingdom is to be converted, we find this provided for by the ferment ptyalin, secreted by the salivary glands. The action of ptyalin is similar to that of the ferment of the pancreas, known as amylopsin—in fact, the latter provides for, or disposes of, much work that is left uncompleted by the former. The sweet taste of bread, noticed by those blessed with an abundant secretion of healthy saliva, is due to the transmutation of a portion of the cooked starch and dextrin, contained in the bread, to glucose.

The process of cooking, as is well known, brings about preliminary changes which greatly facilitate the action of the digestive ferments. Therefore, man, the "cooking animal," possesses advantages over the rest of living beings, because he pursues the most fruitful and economical methods of preparing food for conversion into a readily assimilable condition.

The action of the salivary ferment being confined almost wholly to starchy matters, the portions of food consisting of proteids depend for their conversion into soluble, crystalloid or assimilable forms upon the action of the gastric and pancreatic secretions.

Considering the gastric secretion first, we find several distinct ferments present. One of these has the property of curdling milk, as we know from the use of rennet. Another, and a highly important one, pepsin, is devoted to the conversion of proteids, hence the term proteolytic action. In this class we include such bodies as albumin, syntonin, globulin, casein, fibrin, the albuminoids, etc. In taking up this subject of peptic digestion we consider:

1. The reaction and properties of pepsin.
2. Its mode of action.
3. The products of peptic digestion.
4. Manufacture of commercial pepsin.
5. Pepsin testing.
6. Its application as a remedial agent.

Properties of Pepsin.—In a condition as pure as has been obtained, pepsin is shown to be a colloid, differing from albumin in its reaction with nitric acid; it does not give the xanthoproteic reaction (yellow on heating), is not precipitated by acetic acid and potassium ferrocyanide, nor by tannic acid, mercuric chloride, silver nitrate or iodine. When in solution its activity is destroyed by heat at temperatures above 160° F.

With reference to its mode of action, it may be said that the changes produced in bodies with which it comes in contact are not yet very clearly understood. The energy displayed by ferments in general has been happily compared by Dr. Roberts, as, in its nature, resembling the mode of motion displayed in the magnet, and which is capable of exciting a similar condition or molecular disturbance in other bodies subjected to its influence. The action of the peptic ferment is entirely superficial. This is the natural result of its being a colloid. It cannot permeate or infiltrate the substance to be acted upon, because albumin and foods containing albumin, such as eggs, meat and many vege-

table matters, are, when cooked, in the nature of a septum analagous to parchment paper, into which the pepsin cannot readily penetrate or be absorbed; so that its work consists essentially *in a wearing away of the surface.* A better use should be made by the eater, of the knowledge that the action of pepsin is superficial. Increase the surface to be acted upon by thorough mastication or other methods. The advantage of increasing the surface of food to be exposed to the digestive fluids by proper comminution has long been recognized; in fact, in what may be called pre-scientific times. The grinding of grain, the chopping of meat, as in the case of sausages and hash, mashed potatoes, etc., are all a practical recognition of the necessity of dividing the food well, so as to enlarge the surface acted upon.

The difference in the amount dissolved under the opposite conditions supposed can be happily illustrated by the process of dissolving rock candy in water. In two separate portions of water stir respectively an ounce of this form of sugar in lumps and an equal amount in powder. The results convey an instructive lesson, applicable in ordinary nutrition in the use of digestive ferments and in testing them.

As stated further on, the products of gastric digestion are complex, consisting in addition to undigested food, of syntonin, or acid albumin, and various peptones.

Considering the manufacture of pepsin, we have gradually advanced from its preparation in the crudest form, by scraping and drying the mucus from the inner lining membrane of the animal stomach, to products which are entirely soluble, nearly odorless, permanent and extremely active. Various pepsins were here shown to illustrate the progress made in purity, digestive power, freedom from odor, and other sensible properties, while some of the tests showed that a degree of activity had been reached enabling 2000 parts of coagulated albumin to be digested by one part of dry pepsin. The superiority of the present processes of manufacture depends upon a previous solution of the pepsin in a feebly acid liquid, and its purification from contaminations, such as mucus, by appropriate means. To Scheffer is due the credit of first practically developing this improved method of manufacture. An extract from minced stomachs, by 1 per cent hydrochloric acid, was here subjected to filtration, with the result of obtaining a turbid liquid. The lecturer now showed how admirably *purified* talc was adapted to securing a perfectly clear filtrate. Ordinary commercial talc contains iron, which, as will be demonstrated later on, seriously impairs the proteolytic power of the product, hence the importance of using only the purified article. The separation of the crude pepsin, in the form of a magma, by salt in excess, was also shown.

The testing of pepsin was next demonstrated with an exhibit of appropriate apparatus for examinations on a large scale. Particular stress is to be laid on an accurate and uniform division of properly coagulated albumin. If forced through a sieve of 30 meshes to the linear inch with a spatula, it is obtained in a satisfactory state of comminution. On this point the Pharmacopœia is not explicit, nor does the acidity of the test liquid therein specified approximate sufficiently to that of the gastric juice. The average amount of absolute hydrochloric acid should not be over 0.2 to 0.3 per cent., whereas the pharmacopœial percentage is 0.48.

In its application as a remedial agent prescribers have had to encounter many perplexing questions. What should be the dose of pepsin? When should it be administered? What are its incompatibles? These questions have to a large extent been solved. There is no doubt but that the prevalent doses of pepsin have been altogether too small and entirely disproportionate to the results expected. Owing to the improved methods of testing pepsin, we are now in a position to correctly indicate the dosage.

The proper time for administering pepsin, under ordinary conditions, is from one to two hours after meals, when sufficient acid has been secreted to render it operative. If desirable to administer it immediately after meals it should be accompanied by lactic or hydrochloric acid.

Lactic acid is now generally conceded to be produced from food matters, as it is not a constant constituent of the gastric juice. Hydrochloric acid, on the contrary, is uniformly present in health, being derived from the chlorides, and absent only in certain diseased conditions. This dissociation of the chlorides takes place in the pyloric glands.

Concerning incompatibilities, quite a few of the commonly prescribed remedies exert an inhibitory effect. Apart from any possible action on the mucous membrane during digestion, when a decided nervous tension may be said to exist, certain medicinal agents interfere with the action of pepsin itself. Thus, mercuric chloride was shown, in the test submitted, to have interfered materially with the peptic power. Also ferric chloride notably decreased the amount of dissolved albumin.

Alkaline substances, such as the bicarbonates, in combination with pepsin, are immediately destructive to it in the presence of water. If pepsin be first treated with

sodium bicarbonate and the solution afterward acidified it will be found to have lost its digestive power.

From what has been said it is easy to infer the proper time for administration of medicinal agents known to have an inhibitory effect. They should be given only when gastric digestion is well under way or nearly completed.

Considering finally the pancreatic secretion, we find it composed of a number of distinct ferments active in an alkaline medium and capable of disposing of or converting not only amylaceous and albuminous food, but having also an action on fatty substances by which the latter are rendered easy of absorption.

Amylopsin promptly converts starch paste into glucose and thus supplements the action of the salivary ferment; trypsin, capable of acting on proteids, ranks in importance with pepsin itself, and the products of its proteolytic action, peptones, deserve an especial consideration.

Peptic digestion usually results in an incomplete conversion of proteids into peptones. Syntonin or acid-albumin (bearing about the same relation to albumin that dextrin does to starch), is almost always present in the final gastric tssue. and the provision for its ultimate conversion to peptone exists in the presence and action of trypsin itself.

A very servicable application of pancreatin is in the preparation of predigested foods—that is, foods capable of immediate assimilation, and in which the proteids and starchy matters are presented as peptones and glucose.

As an illustration, we may take peptonized milk, prepared by warming a pint of milk with 4 ounces of water, 5 grains of pancreatin and twenty grains of sodium bicarbonate, for half an hour, at a temperature of about 120° F.

The occurrence of a slight bitter taste offers a sufficient indication of the proper time to end the process. Pancreatin is preferable to pepsin for this purpose, because the latter always results in causing a degree of bitterness verging on the unpalatable.

Pancreatin should be administered shortly before a meal, if it is desired to obviate its possible contact with, or exposure to, the gastric juice. In contact with acid and pepsin—a condition it must at certain times encounter in the stomach—it is destroyed.

Peptones show interesting reactions. They are not coagulated by heat or by nitric acid. The latter, however, when aided by heat, produces what is known as the xanthoproteic reaction. This color reaction is undoubtedly familiar to every one whose fingers have been stained by strong nitric acid, and where ammonia, the neutralizer, has heightened the effect.

A recent application of pepsin and pancreatin in the removal of diphtheritic and croupous membranes has resulted from the perfection attained in the quality of the digestive ferments.

The membranes or false tissues are dissolved, just as would be the case with meat or fibrin. Pancreatin in an alkaline solution, and pepsin in an acid liquid, both of liberal strength, have been used with marked success.

[FROM THE MEDICAL AGE, FEB. 11, 1889.]

NOTE ON PEPSIN IN DIPHTHERIA.

BY DR. A. C. WILKINS, OSKALOOSA, IOWA.

Patient, young man; 30 years of age. He was attacked with malignant form of diphtheria, engrafted upon an old catarrh.

The membrane covered the entire fauces, was thick, ash colored, and leathery; it was completely dissolved or digested by P., D. & Co's pepsinum purum pulvis in twelve hours time.

The catalytic changes commenced almost immediately after the pepsin was applied, it being used in an insufflator.

I have used the pepsin in a number of cases with equally good results.

I claim that by dissolving the membrane with pure powdered pepsin that reabsorption and contamination of the system, of the diphtheritic poison is prevented.

The pepsinum purum pulvis, on account of its higher digestive power, its solubility, its pasty and adhesive properties, when brought in contact with a moist or dampened surface, gives it an advantage over every other form or make of pepsin, for dissolving diphtheritic membrane. It may be blown through a tube or quill.

[Reprinted from Druggists' Bulletin, Sept. 1888.]

Comparative Pepsin Testing.*

BY F. A. THOMPSON, Ph. C.

Pepsin is a drug which is conceded to be one of the most important of our materia medica, and it is with a view to determining the true and relative value of the various makes in use that I present this paper in as concise a form as possible, on the subject of comparative pepsin testing.

Reviewing the tests laid down in the different pharmacopœias and in the recent issue of the National Formulary, I find a great variance in the conditions, as can readily be seen at a glance, in the schedule given below. The three Pharmacopœia tests may be criticised on the point that an excess of acid is used, *i. e.*, far more than in the gastric juice.

It is not my intention to criticise the value of these various official tests, as they are intended only for the purpose of determining whether a pepsin is above or below the requirement of that test; but I hope to show that the usual application of any one of these tests in determining the comparative proteolytic action of various pepsins, gives fallacious results.

The prevailing rule in making comparative tests of pepsin, is to use the same amount of albumen, water, acid and pepsin, all being subjected to the same temperature and treatment during a like period of digestion. This apparently prescribes like conditions, but here comes in the fallacy, for the conditions so soon become unlike during the test, that the comparative result is vitiated.

SCHEDULE OF VARIOUS TESTS.

Tests.	Parts of water to one part of albumen.	Percentage of absolute HCl.	Period of Digestion.	Temperature—Farenheit (Celsius).	Treatment during Digestion.	Requirements for one part of pepsin.	Condition of Albumen.
U. S. P. 1880.	10	0.47	5 to 6 hours.	100° to 104° F. (38° to 40°.)	....	Should digest at least 50 parts.	....
Brit. Ph. 1885.	4.5	0.38	30 minutes.	130°. (54.4°.)	Well stirred.	Will dissolve 50 parts.	Albumen through a wire gauze of 36 meshes.
Germ. Ph. 1882.	15	0.40	5 to 6 hours.	104° (40°.)	Often and violently shaken.	Dissolves 100 parts to an opalescent solution.	Albumen in pieces the size of a lentil.
Natn'l Form'y 1888.	10	0.16	60 minutes.	125°. (51.6°.)	Shaken well at intervals of 5 minutes.	To dissolve 500 parts, which is ¾ the amount taken.	Through a No. 36 hair sieve.
Author's Modified U. S. P.	10	0.30	6 hours.	Constant at 104°. (40°).	Constant and uniform stirring.	Shall promptly digest the amount taken.	Albumen through a No. 30 brass sieve.

* Read before the American Pharmaceutical Association, Detroit, September, 1888.

The usual result of such a test is that one brand has nearly or completely digested the entire amount of albumen taken, and the rest have only digested various fractions of the amount of albumen originally taken, which shows that the pepsins have a different proteo, lytic action, *but does not represent the true comparative action of the various digestive ferments.*

The fallacy of such a test lies in the fact that the conditions are not the same when one pepsin completely digests the total albumen subjected and the others digest only fractions of the same. For the action of pepsin being only superficial, the weaker pepsins soon have more surface of albumen to act on than the stronger, and therefore show better than they should. The reasons for this reside in the fact that an increase in the proportion of albumen to that of pepsin increases its digestive power as the surface of albumen has been increased.

I claim that the only proper way to determine the true comparative proteolytic action of pepsins, *is to take sufficient of each pepsin to completely digest the same amount of albumen under exactly like conditions, or use sufficient of each to digest the same per cent. of the total albumen taken.* In testing pepsins, we cannot accept that there is as much ferment in one grain of one product as there is in the same amount of another, so the only correct way is to take for a basis of calculation, what a pepsin of high digestive power can do in a given time, and call this for convenience, 100 per cent., and then determine by comparative assays, how many grains of the other makes under examination, it requires to do the same amount of work or completely digest the amount of albumen taken, stating the results in per cent.

This can be explained in a simple way, for example, (A) by digesting 5 grains of one pepsin with 500 grains of egg albumen in 11 fluidounces of acidulated water, containing 0.3 per cent. of absolute hydrochloric acid, and 5 grains of another sample subjected to like conditions for an hour. At the end of this time we find that the former sample has completely digested the albumen taken, while the latter has failed to dissolve completely the albumen taken, or about *90 per cent. upon weighing* the residue, showing that there is a difference by this test in their digestive power. Example (B). Now, if 3 grains of the former and 5 grains of the latter are taken and subjected to the same conditions as the foregoing, if it be found that at the end of an hour and a half, that both samples have nearly completely dissolved the entire albumen, it indicates that there must have been as much *active ferment in 3 grains of the former as there is in 5 grains of the latter*, and calculating this out in per cent., we would say that the latter contained $\frac{3}{5}$, or *60 per cent.* as much ferment as the former sample.

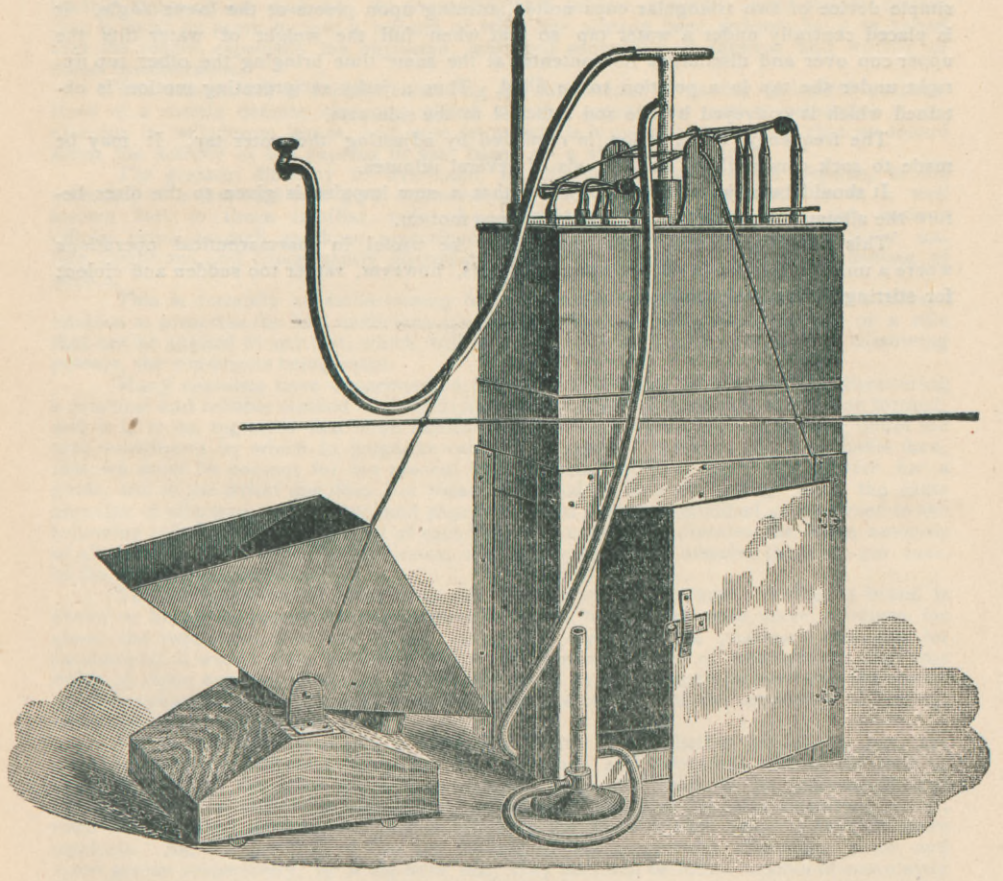
By experiment (C) I wish to show how dissimilar results in digestive power can be obtained from the same pepsin. If one part of a pepsin of high digestive power, such as possessed by the one experimented with, is allowed to act upon 2000 (1), 2500 (2), 3000 (3), 4000 (4) parts of albumen for six hours by modified U. S. P. test, (see schedule) it is found that the 2000 grains have been completely digested, and weighing the residue in the others, No. 2 has digested 2400 parts; No. 3, over 2700 parts and No. 4, fully 3400 times its weight of albumen in the same length of time. Now we have four digestive powers ranging from 2000 to 3400, and which one of these are we to accept as the true digestive power of this sample?

Why are such different results obtained by this test? The reasons are that in all above the 1:2000, there has been different per cents. of excess of albumen exposed to the action of the ferment, and as an increase of the proportion of albumen to the pepsin increases the digestive power, the cause of the above results is easily explained.

If the results of the foregoing experiment are compared optically with those we have when comparing various pepsins by an official test, and also with the florid advertisements in the form of photographs which are intended to show the comparative strength of various pepsins, the similarity is very striking, and illustrates the principle that the weaker pepsins have an advantage over the stronger in having an excess of albumen to act upon, in propor-

tion to the actual amount of ferment contained in them, otherwise they would have completelv digested as much as the stronger sample.

In testing pepsins, the change of temperature and amount of stirring during digestion being important to reach any uniformity of results from day to day, I have used an improved apparatus, devised to give a constant temperature and fairly uniform stirring, a description of which I give, as stated by Chas. E. Parker, Ph. C., in the "DRUGGISTS' BULLETIN" of May, 1888.



APPARATUS FOR TESTING PEPSIN.

The apparatus consists of a water bath with an attachment for agitating the mixture under examination.

The water bath is constructed to receive twelve large test tubes (5 ozs), in which are placed the mixtures for artificial digestion. The heat of the water bath is maintained within half a degree of constancy by a Reichert thermo-regulator automatically controlling the gas supply. A thermometer is inserted in the bath to indicate the temperature.

Over the cover of the bath is balanced a rocking frame to which twelve glass rods are suspended, in sets of six, so that they have an equal up and down motion of about two inches. These rods hang in the test tubes when in position, and each has secured to it by friction two discs of thick sheet rubber a little smaller than the tubes, one being at the lower end, the other two inches above it. The stirring is effected by the motion of the rods and discs.

The rocking frame is actuated by a motor which should be placed in the sink and is connected by a stiff rod to a side arm on the rocking frame. This motor is a simple device of two triangular cups united, turning upon pivots at the lower angle. It is placed centrally under a water tap so that when full the weight of water tilts the upper cup over and discharges its contents, at the same time bringing the other cup upright under the tap in a position to be filled. Thus a jerky reciprocating motion is obtained which is conveyed by the rod attached to the side arm.

The frequency of its action is regulated by adjusting the water tap. It may be made to rock constantly or at intervals of several minutes.

It should be adjusted to act so often that a new impulse is given to the discs before the albumen has subsided after the previous motion.

This simple and cheap little motor may be useful in pharmaceutical operations where a uniform motion is not indispensable; it is, however, rather too sudden and violent for stirring during evaporation.

[FROM THE MEDICAL AGE, JAN. 25, 1889.]

COMPARATIVE ACTIVITY OF PEPSINS.

BY F. A. THOMPSON, PH. C., DETROIT, MICH.

Probably during the past few years, no subject has received more attention from prominent chemists than pepsin, which carries force as an argument that it is one of the leading drugs of our materia. In presenting this subject it would seem almost certain that it must be more or less a resumé of what has already been written, but it is hoped that the reader, especially the physician, may find something of interest and worthy of some consideration.

The present era is rapidly conceding the importance of having galenical preparations of a certain definite strength, based on the amount of active principle, *e. g.*, atropine in belladonna leaves, and now let us ask, is it not just as essential that we should know the activity of the pepsins in use, based on a similar standard?

The greatest difficulty to overcome, in adopting a *standard* for pepsins, is the selection of a test that will give impartial and more uniform results. It is a well known fact to those familiar with the examining of pepsins, that the various official tests, as well as those prescribed for some special brands, give entirely unlike conditions and consequently discordant dissolving powers for the same sample of pepsin.

This is certainly an embarrassing fact to face the practicing physician who is always anxious to prescribe the best medicines attainable. What we sadly need, is a test or a rule that can be applied to any test, which will give approximately the comparative dissolving powers, the conditions being equal.

Many chemists have experimented for some time past, with a view of discovering a practical and reliable method of determining quantitatively the amount of peptone formed, and it is to be regretted that none satisfactory has been found, as it is without doubt the true constituent by which to judge the value of a pepsin. It seems highly probable then, that we must be content for the present with the comparative dissolving powers for a guide, and to the writer this does not mean the usual method of testing, when the same amounts of albumen, acid, water, and pepsin are used but when modified or subjected to the following rule:* "Take sufficient of each pepsin to completely dissolve the same amounts of albumen under exactly like conditions, or sufficient of each to dissolve the same per cent. of the total albumens taken."

The official as well as other tests are satisfactory to determine whether a brand is above or below its respective requirement or claim, but as we now have products far above the requirements of the official standards, especially the pharmacopœia test for saccharated, it would seem desirable that we have some means of determining the true value of these superior products, and to this end I would earnestly request that the reader try the application of the above rule, and compare the results with the usual way of testing, other conditions being equal.

I hold that the above rule is applicable to any test, whether official or not, the only requirements necessary, are, that the conditions and treatment during the time of digestion shall be the same for each container. I do not wish to be understood that the application of the above rule to two unlike tests will give the same dissolving power, even for the same sample, but, that it will give the same *relative* value of two or more products. As, for example, if two are capable of just completely dissolving 2,000 and 1,200 grains respectively, by a six-hour test, they also will be found capable of completely dissolving about 165 and 100 grains respectively by a one-hour test, other conditions being the same.

The reasons for using various amounts of pepsins, are that we can't accept that there is as much active ferment (or active principle) in one grain of one product as there is in the same quantity of another; second, that pepsins act entirely superficially, so the more surface of albumen exposed the more the same amount dissolves; third, that the ferment is not destroyed by dissolving albumen, and consequently dissolves more rapidly in the first than in the last stage of the test. After carefully considering these points, it certainly must seem obvious why different amounts of various pepsins should be used to

* From paper on "Comparative Pepsin Testing," by the writer, read before the A. P. A., September, 1888.

dissolve exactly like amounts of albumen, if we wish to give each one an impartial basis to establish its peptic value.

In my experience in pepsin testing, I have never found it practical or satisfactory, and often impossible, to try to estimate the amount of undissolved albumen, by filtering, drying and weighing the residue. When a solution, containing partially dissolved particles of albumen, is thrown upon finely scraped asbestos, in a Goosch filter, attached to a strong filtering pump, it will immediately become clogged by these particles, and further filtration rendered impossible, at least so slow as to be practically useless. For this reason I have never been able to use the test given by the new National Formulary. I have, however, estimated the amount of undissolved egg-albumen, by immersing the container or tube in cold water (40° to 50° F.) and removing the supernatant fluid by decantation, but as this requires a day or two to complete, I considered it impracticable; therefore, I have always taken a complete solution of the albumen as a basis or standard requirement. It is also desirable in pepsin examinations to use a standard for control. as I have sometimes experienced mysterious results, which I could not account for, and might have accepted the results as satisfactory, if I had omitted my standard, which acts as a check. I might add here that I am disposed to believe that the nearest pure pepsins I have handled deteriorate after some time, and, therefore, one must closely watch their standard.

For convenience of computing, I selected from the many samples I have examined, the one having the highest digestive power (sample number 1 in table) and called it a 100 per cent. pepsin, which does not mean that it is absolute, as such a product is unknown. Then by repeated assays, I ascertained how much of the other samples it required to completely dissolve the same amount albumen as the standard, under the same conditions, and from this calculated the per cent. of active ferment.

In conjunction with these notes I have decided to publish in tabular form the comparative activity of the leading brands found in the market, the results being based on the foregoing.

This summary represents six scale and four powdered products arranged in accordance with dissolving powers.

As previously stated, I have also used a standard on the basis of 100 per cent. which was a soluble pepsin in large scales and possessing a high digestive power. I would beg to add here in justice to the manufacturers of this highly potent product that it was made by PARKE, DAVIS & CO. and known under the name of *pepsinum purum in lamellis.*

In reviewing the table one finds a great difference in activity and that some do what is claimed, while others come far from it, when subjected to a comparative test.

The various strengths stated are based on repeated assays, conducted in a most careful and satisfactory manner by the use of an improved pepsin tester* and the following general rule which can be modified to suit the convenience of the experimenter but without changing the conditions of test.

Preliminary Test: Boil the eggs 15 minutes, cool, and after removing all the yolk and superficial moisture, press the coagulated albumen through a No. 30 brass sieve by means of a stiff spatula. After thoroughly mixing the finely divided albumen, 10 grams are carefully weighed out and transferred to a medium sized mortar; then 95 c. c. of distilled water previously warmed to about 100° F., are measured out and small portions added to the albumen in the mortar and the mixture carefully triturated to ensure uniform division of the particles and finally transferred by means of the remaining water to a large test tube (capacity about 130 c. c.) having a flat bottom. Add 5 c. c. of 6 per cent. hydrochloric acid (s. g. 1.0296 at 59° F.) and place the tube in the water bath and when the temperature reaches 104° F. (40° C.) various amounts of the pepsin under examination are added and the mixture subjected to a constant temperature and fairly uniform shaking for six hours. When examining soluble pepsins I have found it more convenient to make a solution of definite strength substracting the amount of pepsin solution taken from the amount of water added to each tube. After digesting the required time, the tubes are removed, filled with ice cold distilled water, immersed in very cold running water, and after one-half hour they are taken out and placed in a suitable rack in order of their digestive power, *i. e.*, from the lowest to the highest proportions.

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* Druggists' Bulletin, May, 1888.

SUMMARY OF COMPARATIVE PEPSIN EXAMINATIONS.

NUMBER.	PHYSICAL PROPERTIES.	CLAIMS FOR ACTIVITY ON THE LABELS.	ACTUAL (COMPARATIVE.) DISSOLVING POWER OF ONE GRAIN.	COMPARATIVE VALUE REPRESENTED IN PER CENT.
1.	Semi-transparent, permanent scales, readily soluble and free from objectionable odor or taste.	Will completely dissolve 2,000 times its weight of albumen in 6 hours.	2000 grains.	100 per cent.
2.	Opaque, amber scales, putrefactive odor and comparatively insoluble.	Will dissolve 1,000 grains in 4 hours	1200 "	60 "
3.	Yellowish scales, strong putrefactive odor and exceedingly hygroscopic.	Will dissolve 700 to 1,000 grains in a few hours.	1000 "	50 "
4.	A permanent sparingly soluble, gray powder, and quite odorless and almost tasteless.	Will dissolve 1,000 to 1,450 grains in 4 to 6 hours.	750 "	37.5 "
5.	A light colored, permanent powder, largely soluble.	Unequalled in digestive power.	350 "	17.5 "
6.	Soluble amber colored scales, nearly odorless, but very hygroscopic.	A potent and speedy solvent of albumen.	250 "	12.5 "
7.	Permanent, readily soluble and almost colorless scales		200 "	10 "
8.	Permanent, grayish and soluble powder; odor suggestive of lactated compounds.	Will dissolve 250 to 450 grains raw beef in 6 hours.	200 "	10 "
9.	A soluble grayish powder; odor suggestive of lactated compounds.	None on activity.	200 "	10 "
10.	Almost transparent, soluble scales quite free from odor and permanent.	Will dissolve 535 to 600 parts of albumen speedily.	50 "	2.5 "

The tube found next in order to the last one free from albumen, is accepted as near the true dissolving power of the sample.

After making the preliminary test, a second or more accurate one must be made, *i. e.*, under the same conditions and treatment, but using amounts of pepsin, nearer the proportion found in the preliminary test, reading the results in a similar manner, which will indicate the amount of albumen the sample is capable of completely dissolving.

Dec. 1888.

PEDIATRIC POINTS AND PICKINGS.

Among some interesting notes on the treatment of diseases of children which Dr. I. N. Love, of St. Louis, has grouped under the above heading, in the *Weekly Medical Review*, Jan. 26, 1889, p. 97, is the following on pepsin in diphtheria:

The application of pepsin to digest away the membrane in diphtheria and membranous croup is not new, and is more or less commended and resorted to by physicians in the treatment of these diseases.

Naturally, however, its utility depends entirely upon its digestive activity, and on account of the many preparations of pepsin of feeble or no digestive power heretofore at the disposal of physicians the results obtained have been in some cases discouraging.

As to the value of pepsin, however, in these affections, when of proper purity and strength, there can be no question. We believe that the recent improvements in pepsin, securing greater purity, strength and permanence (we allude to the pepsinum purum in lamellis of Parke, Davis & Co.,) will lead to its extensive use in diphtheria and membranous croup, maladies now attended with such grave results even when combatted by the most expert medical care.

[FROM THE DRUGGISTS' BULLETIN, DEC., 1888.]

PEPSIN AND ITS CONGENERS.*

BY J. LE ROY WEBBER, PH. G.

Gentlemen: The digestive ferments are now so extensively employed, and with such acknowledged benefit in the treatment of disease, that their study is well worthy of your attention.

The term ferments seems to have been unfortunately or unhappily chosen to designate this class of bodies and is frequently misleading to the student. This arises from the fact that our usual conceptions of fermentation are connected with some such substance as yeast and physical phenomena attended with the disengagement of gas and a splitting up of sugar into alcohol and other bodies. In science, however, the word ferments has come to cover a class of substances which exercise merely an action designated by some as catalytic, meaning that they produce certain changes simply by their contact or presence, without themselves undergoing any notable change.

Regarding the mode of action of pepsin and unorganized ferments generally, a very beautiful comparison has been employed by Dr. Wm. Roberts. I consider it a much happier illustration than referring it to catalysis and will here quote from his work:

"The digestive ferments are all the direct products of living cells, and may be regarded as the repositories of cell-force. They are quite unknown in the domain of ordinary chemistry. Their mode of action bears no resemblance to that of ordinary chemical affinity, and has a distinctly physiological character. They do not derive their marvellous endowments from their material substance. They give nothing material to, and take nothing material from, the substance acted on. The albuminoid matter which constitutes their mass is evidently no more than the material substratum of a special kind of energy—just as the steel of a magnet is the material substratum of the magnetic energy—but is not itself that energy. This albuminoid matter of the ferment may be said to become charged at the moment of elaboration by the gland-cells, with potential energy of a special kind—in the same way that a piece of steel becomes charged with magnetism by contact with a pre-existing magnet. The potential energy of the ferment is changed into the active form (*i. e.*, becomes kinetic) when it is brought into contact with the alimentary substance on which it is designed to act."

Unorganized ferments are distributed very widely throughout the vegetable and animal kingdoms, and, while acting on the utmost variety of organic substances, their chief function appears to be the conversion of insoluble matters into soluble forms in which they are capable of assimilation.

Thus the plant converts, by appropriate ferments, its store of starch into soluble glucose, which can then be readily transported to the point where it is needed for cell growth or tissue elaboration. These ferments, while adapted to certain purposes, and conducive to the welfare of the plant, do not always affect the human organism in a kindly manner. Thus many fruits, tubers, roots, barks, cereals, etc., contain a lactic or other ferment which is often capable of producing injurious effects when the substances containing it are partaken of in an uncooked condition.

A noteworthy point of dissimilarity between the greater part of the vegetable kingdom and animals is, that in the former we find, in opposition to the law of gravitation, and by means of capillary attraction, osmosis and evaporation, the juice or sap is drawn in an upward direction from its first source, the earth; while in animals, on the contrary, the food is usually elevated first, and in obedience to the natural law pursues a downward course.

What happens in this downward course, and at the way stations, it will be my task to explain to the best of my ability, and consistently with our present knowledge of the subject.

Now, gentlemen, it will be well for us to consider the action of unorganized ferments without reference to any connection or interference of any vital force with these processes. I am justified in saying that these processes are largely mechanical and physical. They hardly deserve the term of chemical actions, being rather of a quasi-chemical nature.

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* A lecture delivered on invitation before the faculty and students of the Detroit Medical College, Dec. 5th, 1888. Reported especially for The Druggists' Bulletin by H. F. Meier.

To begin, then, with a consideration of the operations taking place in the alimentary canal, we first must consider the action of the saliva. This fluid contains a ferment named ptyalin, very similar to the diastase of vegetables, which is concerned chiefly in a preparatory conversion of starchy matters. This ptyalin is most active in feebly alkaline media; and, indeed, the healthy human saliva has a feebly alkaline reaction. That the action of ptyalin is in general only transient and incomplete, must be evident when we consider that it is destroyed in the gastric juice. The work thus begun and arrested is, however, completed by ferments derived from the pancreatic glands, which we will consider later on.

We will now take up the question of pepsin, which merits our careful investigation.

The gastric juice contains in reality two distinct ferments, one of which curdles the casein of milk, as I have here shown you by adding a small quantity of pepsin solution to warmed milk; and the other has the more important property and power of converting into soluble forms such food-matters as fibrin, albumin, and albuminoids generally. As these are classified as proteids, the term proteolytic action has been applied to both this effect of pepsin and also to a similar effect of trypsin, one of the pancreatic ferments.

I have here a number of flasks in which the solvent and digestive action of pepsin is illustrated, showing also the interfering effects on digestion, of various medicinal agents which are very commonly prescribed. Here is also a control-flask for the purpose of comparison. In each one we have 100 c. c. of water containing 3–10 per cent. of hydrochloric acid (absolute),* to which I have added 10.0 grams of albumen and 5 milligrams of pure pepsin. They have been digested for a period of six hours at a temperature of 104° F (40° C.).

Before going further I wish to direct your attention to the preparation and treatment of the albumen. Sound, fresh eggs have been boiled for 15 minutes, placed in cold water, and, after being wiped dry from superficial or exuded moisture, the albumen is forced, by means of a spatula, through a sieve having 30 meshes to the linear inch. This insures a uniform subdivision of the albumen. A few explanatory words about the purity of the pepsin itself may not be amiss. We have never yet been able to obtain pepsin as a distinct principle in a state of absolute purity; and, indeed, the same may be said about ferments generally. They are all contaminated, in a greater or less degree, with substances which are themselves inert, but present almost insurmountable difficulties of separation, since the ferments themselves are exceedingly delicate and unstable, and do not bear rough handling as would occur in the interaction of ordinary chemicals.

In the case of the pepsin here employed, a high degree of purity has been attained as is evidenced by its behavior in the control flask, where it has dissolved and partially converted into peptone 2000 times its weight of coagulated albumen. It is capable, indeed, of doing more than this under favorable conditions. These conditions it is well to understand and apply, particularly in the testing of pepsins. I have here repeated parallel experiments, first made by Prof. Baden Benger, and which demonstrate two important points: First, that the action of pepsin is entirely superficial; and secondly, that the amount of syntonin and peptone formed is largely dependent on the amount of albumen present, whether this be in excess or not, that is, as proportioned to the pepsin used. In these two flasks we have respectively 100 grains and 1000 grains coagulated albumen, the acidulated liquid (5 ozs.) containing besides in each case exactly $\frac{1}{20}$ grain pepsin; while in the 100 grain flask the albumen is just entirely dissolved, a comparison of the other with a control flask containing merely the albumen with acidulated water (minus pepsin) shows that a much larger quantity of the albumen has dissolved, as is demonstrable to the eye alone. Were I to weigh the undissolved residue of albumen I would undoubtedly get a result corroborative of Prof. Benger's. In his case while 100 grains went into complete solution in one flask, the undissolved residue in the other weighed only 220 grains, showing 780 grains to have been dissolved.

A practical application in dietetics may be made of this knowledge, as showing the importance and value, especially to enfeebled digestion, of proper comminution, whether this be performed by mastication or other means of subdivision, a matter which is too often neglected by the laity.

I will next call your attention to the inhibitory effect exerted by several medicines and which must occur when they are administered at improper times, that is, immediately before, during, or too soon after a meal, before the digestive process can be considered as fairly established and under way. To the contents of this flask, otherwise identical with the control, I have added 1 minim tincture of iron to the 100 c. c. The

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* Equivalent in round numbers to 1 per cent. of U. S. P. acid which contains 31.9 per cent. gas.

amount of albumen undissolved will show you to what extent ferric chloride is capable of interfering with digestion. The next flask, instead of acidulated water, contains a one per cent. solution of sodium bicarbonate; here you see the pepsin is rendered incapable of accomplishing anything and the albumen is entirely undissolved. The moral of this experiment would therefore be unfavorable to the conjunction of pepsin and bicarbonate of sodium, which is quite a favorite prescription in infantile cases. A single experiment of this kind will convince the physician that such an association of pepsin with alkaline substances is irrational and destructive to the pepsin, as nature has intended and permitted it to act only in an acid medium. After the pepsin solution is once rendered alkaline, addition of hydrochloric acid fails to restore its activity. The next flask shows the inhibitory effect of mercuric chloride 1:5000. While this does not very seriously interfere, it nevertheless exerts some deleterious action. It may here be pointed out that most substances which rank high as antiseptics have also the property of delaying or seriously inhibiting the action of pepsin.

In this last flask, I have perhaps the most important and interesting experiment, as it is a remedy which is almost universally employed. I have here, in addition to the usual ingredients, two grains of ammonio-citrate of bismuth. You will observe that the albumen is entirely dissolved, while the white turbidity is due to the formation of oxychloride of bismuth from the soluble ammonio-citrate at the moment it is brought into contact with hydrochloric acid. This action occurs, of course, also in the gastric juice. The albumen has here gone into solution because the bismuth salt has been brought into contact with the pepsin in an acid medium. Were this to take place, however, in a feebly alkaline solution, which is almost invariably the case in elixirs of bismuth and pepsin, the peptic power would be destroyed. Even in neutral solutions carefully prepared, the soluble bismuth salts, and, in general, the salts of the heavy metals, sooner or later, exert an injurious effect. The conclusion to be herefrom deduced would therefore be, to give the pepsin and bismuth separately, or else mix them in a feebly acid solution. The latter course always results, however, in an unsightly mixture.

Now, a few remarks as to the general properties of pepsin and we will then consider the products formed during peptic digestion. Pepsin is a colloid and differs from albumen by not giving the yellow xanthoproteic reaction with nitric acid. In common with all other known ferments, it is a nitrogenized body, and putrescible under appropriate conditions; its tendency to putrefaction is enhanced by association with peptones, mucus and similar substances, which confer a hygroscopic character. Therefore caution should be exercised in the selection of pepsins, and the sense of smell may be depended upon as a guide in this particular. Any pepsin which presents an offensive odor, even though active, should, for prudential reasons, be rejected, as it is certainly unwise to ingest any substance in which the germs of decomposition are already rife, and which may possibly impart this propensity to food matters and food products in an enfeebled organism, where the secretions are defective and cannot exert the protective action provided in healthy conditions.

We can justly make the following requirements of commercial pepsin: It should be light colored, practically free from odor, soluble in water, and be capable of demonstrating its activity in the digestion of albumen as described. As pepsin is itself freely and readily soluble in water, insoluble pepsin should be rejected as self-condemned, and consisting largely of foreign matters.

The temperature at which pepsin is most active, or when it accomplishes its work in the shortest possible time, is 130° F. (54.5° C.). Like all ferments, it is destroyed completely at temperatures much above a scalding heat. For pepsin, a temperature above 160° F. is sufficient. Alcohol, when in sufficient excess, precipitates it from its aqueous solution.

The products of the action of pepsin upon proteids are various, according to the time and other conditions, being syntonin or acid-albumen, other intermediate grades (parapeptones, etc.), and finally true peptones.

True peptones are soluble in water, are not coagulated by heat, nor precipitated from aqueous solutions by boiling nitric acid. They give the yellow reaction with nitric acid, however, corresponding in this respect with albumen, and are precipitated by mercuric chloride from neutral and feebly acid solutions.

In the digested fluids before us peptonization can be shown to be only partial; thus, if I neutralize a portion of the liquid with sodium bicarbonate solution a precipitate forms showing that syntonin or acid-albumen is still present. An excess of sodium bicarbonate redissolves it however.

The next reaction is an important one and characteristic of peptones. It is known as the biuret-reaction. If to another portion of the fluid from the control flask I now add some solution of caustic soda, and then a small quantity of a weak cupric sulphate solution, you will notice the beautiful crimson coloration appearing, and which is plainly

visible to you against this white back-ground. Fehling's solution can be conveniently employed to produce this reaction.

We will now consider the pancreatic secretion and its properties. This consists of a combination of four distinct ferments, which seem happily designed to supplement and complete the work left unfinished by the ferments of the saliva and stomach. The ferments are varied in their properties and offices. Thus we have: 1. Amylopsin, similar in action to diastase, converting starch into dextrine and sugar. 2. A curdling ferment, acting upon milk in an analagous manner to rennet or the curdling ferment of gastric juice. 3. Trypsin, having powerful peptonizing properties; and, 4. Steapsin, known as the fat splitting or emulsifying ferment. I have here a very thick starch paste, made by boiling powdered starch with ten times its weight of water. You can see how speedily the starch is liquified as I now add a small quantity of powdered pancreatin. The liquefaction is succeeded in a very few minutes by gradual conversion of the starch into dextrin and glucose. I have here a series of jars containing very weak iodine water (about 1:25000). For some time we can obtain a distinct blue color reaction with the iodine water, characteristic of starch. As the conversion progresses, however, the blue coloration becomes feebler and feebler, finally being entirely absent. During the changes the violet-red coloration characteristic of dextrin succeeds to the blue of the starch, and when the conversion into glucose is complete, this also fails to make its appearance.

Now, to demonstrate the presence of glucose in the liquid, which but a few minutes ago was merely a starch solution, I will make use of an extremely sensitive test, namely, a test tablet of indigo (soluble) with sodium carbonate. The demonstration of the presence of glucose depends upon its property of deoxidizing the indigo, thus rendering it colorless by conversion into indigo-white. I will first heat the tube and contents (one indigo tablet and about two drachms of water) to the boiling point and introduce from the tip of this rod a single drop of the converted starch solution. I purposely avoid an excess of the sugar solution here so that you may perceive the gradual fading of the indigo solution as I hold it against this sheet of white paper. You will notice that I have avoided shaking the contents, in which case I would reincorporate oxygen by the admixture of air bubbles, and restore the blue color. Now that decoloration is complete, you can at once see the blue color reappear on shaking, and a repetition of the heating will again decolorize it, if I have sufficient unchanged glucose still present. Chemical agents which bleach the indigo by destructive changes, do not permit of the restoration of the color by re-oxidation.

The ferment which is the chief constituent of the pancreatic juice and of paramount importance, trypsin, also acts to the best advantage in a slightly alkaline medium, the alkalinity of the intestinal secretions being considered as about equivalent to a one-percent. solution of sodium carbonate, the actual secretions of this tract being, however, of a complex nature and permitting also, eventually, of extraneous or putrefactive changes.

A very instructive illustration of the promptness and vigor displayed in tryptic digestion is exhibited in the conversion or digestion of milk. I have here in this water-bath several bottles of milk which have been warmed to about 115° F. On the addition of ten grains of sodium bicarbonate and ten grains of pure pancreatin dissolved in two ounces of water to eight ounces of milk, we can observe the digestion as it proceeds and watch its several stages by testing the liquid with nitric acid. At first this produces a copious precipitate, decreasing in amount rapidly as the action of the pancreatin progresses. I have purposely taken double the amount of pancreatin necessary, to hasten the operation.

The soda and water have been added to prevent curdling, which would otherwise occur on the addition of pancreatin alone to pure milk, owing to the action of the second named ferment.

As the digestion proceeds, you will soon be able to detect a very faint suggestion of a bitter taste, indicating the proper time to end the process, if we wish to use the product as an alimentary substance. This is, indeed, now predigested food, being virtually the peptone of casein with fats and salts of the milk unchanged. You will pereeive how easy it is to prepare such food, which is often of the greatest service in extremely debilitated conditions, when it is advisable to relieve the fevered or weakened digestive organs of the patient or invalid of all unnecessary work. A thermometer is even unnecessary. If the milk employed be first warmed to a little above blood heat, and after addition of pancreatin, soda and water, the bottle or vessel containing it be then placed in hot water to keep up the temperature, the appearance and taste may be noted as a reliable indication of the right moment to check the further action. This can be done by either boiling, which destroys the pancreatin, or by placing on ice, which simply inhibits and yet permits of further action on other food matters, starchy, or of the albuminous or proteid class.

Chopped meat, oysters, biscuit, toast, etc., may likewise be predigested by the aid of pancreatin, and be made to furnish very palatable and nutritive articles of food for the invalid and convalescent. Pancreatin is always selected in the preparation of artificially digested food in preference to pepsin, owing to the fact that the latter gives rise to the formation of certain by-products which are of an exceedingly bitter, unpleasant taste. This taste can often be perceived during eructations from the stomach.

I here apply, a chemical test, nitric acid, showing that the albumen has been converted into peptone, as no coagulation takes place; indeed, trypsin may be said to be the peptonizer *par excellence*, being much superior in this respect to pepsin. It is a curious fact, however, that the properties of the two chief ferments of the pancreas are impaired by long contact with weak acids, and in the presence of pepsin and acid, pancreatin is itself digested and destroyed.

Inasmuch as the action of the fat-splitting ferment is a tedious matter and rather difficult of demonstration, I must for the present forego its practical illustration; enough is, however, known about its action to assure us that the fatty matters are thereby notably comminuted or emulsified, and presented to the lacteals in a favorable mechanical state of division for absorption.

As a consequence of the knowledge which has thus gradually been acquired by patient investigation, we are now in a condition to prescribe these remedies to the best advantage, both by means of a better knowledge of the quantities required, which can not be infinitesmal because the results are commensurate to the quantity employed, and also the time of administration. Pancreatin should be administered prior to a meal or before any acid fluids are secreted in the stomach, which might be prejudicial or destroy it, and pepsin either during or immediately after the ingestion of food, so that it can act thereon in an appropriate menstruum.

When used for the removal of diphtheritic membrane by swabbing, a strong solution of pepsin should be employed in an acid liquid ($\frac{2}{10}$ per cent. hydrochloric acid), or a strong pancreatin solution, the latter always being prepared fresh and containing 2-per-cent. sodium bicarbonate.

The method of insufflating the pure ferments in a powdered form is also highly recommended.

As far as the classification of digestive ferments is concerned, while they are true remedial agents, they cannot with propriety be called drugs, being identical in properties and behavior with the normal secretions of the body.