official preparation of it, though the official spirit contains one per cent. It is often given in the form of the infusion. The common form of administration is that of the oil (dose 1–5 m.), or of the following preparations of it: The Spirit or Essence (*Spiritus Menthæ Piperitæ*) contains ten per cent. of the oil, and there is three and a half per cent. of it in the popular mixture of rhubarb and soda. The dose of the spirit is 0.3–1 c.c. (♏ v.–xv.). Peppermint water (*Aquæ Menthæ Piperitæ*) contains 0.2 per cent. of the oil and is given in doses of 15–60 c.c. (fl. ℥ ss.–ij.). The official troches each contain 0.01 c.c. (about ♏ $\frac{1}{6}$) of the oil. *Henry H. Rusby.*

PEPSIN.—*Pepsinum, U. S. P.* "A proteolytic ferment or enzyme obtained from the glandular layer of fresh stomachs from healthy pigs, and capable of digesting not less than three thousand times its own weight of freshly coagulated and disintegrated egg albumen when tested by the process given below."

Our present knowledge and conception of pepsin have been arrived at by the inevitable, slow, intermittent progress in science, marked by brilliant epochs and retarded and clouded by faulty and incomplete observations and erroneous theories. The investigation of ferments and ferment action has necessarily involved the whole field of problem and inquiry in biology. The history of pepsin, therefore, is found in the voluminous recorded labors of a host of workers. In briefest possible mention it begins perhaps with the first perception by Borelli, three centuries ago (1608–1679), of the existence of secreting glands in the stomach and of the value of gastric juice; then the studies of the gastric juice of regurgitating birds, which established the independence of digestion of mechanical power (an early theory) and of chemical change produced on food (Réaumur, 1752). In 1772 Hunter's observations established the fact of the post-mortem digestion of the stomach by its own juices. It was in 1783 that the first demonstration *in vitro* with pure animal gastric juice obtained by ingenious devices from living animals (Spallanzani) was made. At about this time also were made the first recorded clinical researches in regard to gastric juice as a surgical solvent and as an internal remedy—researches which were inspired by Spallanzani and made by his colleagues, Jurine, Carminati, Senebier, and others. Many interesting and singularly clear and detailed observations are recorded in relation to the gastric juice of beasts and birds, its properties, behavior with various foods, etc., and its action when used as a topical application; and it was observed to have the power "to remove all disagreeable smell from fetid ulcers, to give them a clean appearance, to change the quantity and quality of suppurative matter, and obtain a speedy cicatrization." It was employed thus successfully for tumors, ulcers, gangrene, old sores, abscesses, etc., and internally with benefit in "weakness of the stomach and all those affections produced by faults in this fluid and particularly by its diminution in point of quantity and energy for the purpose of digestion." Very remarkable effects were particularly noted in a "case of gradual emaciation with continual nausea and vomiting."

In 1824 Prout, Tiedemann, and Gmelin discovered hydrochloric acid in the gastric juice. In 1834 Beaumont made his classical observations, and drew the faulty conclusion that gastric juice was the sole digestive fluid and formed gastrites with food. In the same year an impetus was given to the study of gastric juice by Eberle's suggestion and use of infusions from the stomach glands. This led to the brilliant and careful researches of Schwann (1836) upon the active principle of the gastric juice—its behavior, theory of action, method of separation, etc. He gave to this principle the name "pepsin." In 1842 Lehmann published his theories as to the protein nature and cellular origin of pepsin, and its action in the transformation of albuminoids into absorbable substances. Wasmann also put forward at the same time the theory that pepsin is the granular matter of the cell or the substance from which it is formed. In 1857–58 Corvisart and Beale suggested the use of pepsin itself in medicine. In 1864 Hoppe-Seyler classified the various forms of proteids according to their solubility and precipitability by various neutral alkali salts, this classification, by reason of the similarity of pepsin in these respects to other proteids, leading to the present methods by which pepsin is produced by these reagents. Scheffer's suggestion and development of sodium chloride as a pepsin precipitant were inspired by his observations of this reaction of proteins.

Pepsin is now produced from the stomach with the same facility as quinine is made from bark; for, in view of its peculiar origin and nature and susceptibilities on the one hand, it is singularly capable of extraction and utilization in a practical way as an article of commerce. During the last half of the twentieth century, with its accurate, scientific methods of research, and especially during the past thirty years in which pepsin has been increasingly utilized, it, as well as the gastric extract and gastric juice itself, has been the subject of elaborate investigation, and we have now exhaustive data concerning pepsin from a pharmaceutical standpoint.

Great therapeutic interest attaches to the very recent methods of Pawlow for obtaining pure gastric juice from the living animal (dog), to his profound studies thereof, and to the free administration, by Fremont and his colleagues, of this juice in cases of disease of the stomach. They gave it in quantities that sometimes amounted to as much as 500 c.c. per day, and the results which they obtained were at times brilliant. They also used gastric juice as a topical application, noting its solvent, healing and sedative action; this latter quality was also attributed to it when administered internally. Fremont considers this animal gastric juice to be especially adapted to all cases of hyposecretion of the stomach, whether resulting from glandular ulceration, from acute or chronic infection, or from disease of the liver, heart, lungs, and nerve centres. Under its influence dyspeptic phenomena have disappeared more or less promptly, and a remarkable gain in weight and strength has taken place. Patients who have suffered acutely from dyspepsia, and who have become extremely emaciated, have also obtained complete and permanent relief under the use of the remedy.

Pawlow especially calls attention to the fact that gastric juice is now pharmaceutically available as a clinical agent. Others have argued that with a corresponding free use of pepsin and acid similar results may be obtained.

Inasmuch as the healthy stomach of recently killed animals affords a resource for gastric juice in a very concentrated form, rendered perfectly pure by simple means of clarification and filtration, sterile, and free from objectionable odor and taste, there is good ground for the presumption that the fullest therapeutic possibilities of the gastric juice may be realized without the elaborate methods resorted to in obtaining the secretion from the living animal. These observations, which represent the last word of modern achievement in this particular field, give great interest and significance to the early discoveries of Spallanzani and his colleagues, and to the fact that they attracted no further attention and were thus barren of result.

Pepsin is found in the gastric cells of all animals, but the gastric juice of the carnivora is much more powerful in proteolytic action. Pepsin itself, however, has no particular degree of energy or peculiarity of action from any particular source; its "strength" is strictly in ratio to its degree of isolation from the associated non-peptic material of the gastric cell or juice, and from the agents used in its separation therefrom. The pepsin obtained from one creature, therefore, is not stronger than that obtained from another. In the gastric juice of the dog, it is to be noted that the pepsin is associated with a peculiarly high percentage of HCl.

Pepsin is normally associated also with another distinct ferment—the milk-curdling enzyme—which is very energetic in the suckling animal. The ultimate composition of pepsin, the method of its elaboration from the cell, the

mode of its action, and its relation to the other constituents of the gastric juice, proteid, hydrochloric acid, and inorganic salts, have been the subject of laborious research and of speculation, and are receiving increased attention in the progress and practical interest of biological study.

Pepsin is a soluble, unorganized ferment, an enzyme, having the property of converting native proteids into soluble, highly diffusible, non-coagulable proteids. Its action is exerted only in an acid medium, most freely in the presence of 0.2 per cent. absolute acid, slight variations from this not sensibly influencing its action; if the proportion of acid, however, be materially increased—say, to 0.3 per cent.—the enzyme is much enfeebled.

Pepsin exerts freely its characteristic action in the presence of organic acids in general—lactic, tartaric, citric, etc. Notwithstanding the fact that the ferment is so closely and characteristically related to the HCl, the mineral acids in general are not favorable to its action, phosphoric being the only one which approximates at all to the HCl in its affinity to the enzyme; nitric and nitro-muriatic acids are distinctly unfavorable.

Pepsin exhibits considerable activity at a temperature much below the physiological, converting albumen slowly even at ordinary room temperature (60°–70° F.), and its action is completely arrested only at a temperature of about 40° F., and greatly accelerated at 120°–130° F.

Pepsin does not exist preformed in the gastric cell, but is developed from the mother substance, pepsinogen, and under the influence of the acid simultaneously secreted in the gastric juice. This view has for a long time been entertained, and very recently pepsinogen has by Glaessner been prepared free from pepsin and found to be devoid of proteolytic power. This pepsinogen was found promptly to develop into pepsin under the influence of both mineral and organic acids; while oxygen and neutral salts were without effect, and alcohol, ether, and chloroform proved destructive.

"If it be desired to use a diluent for reducing pepsin of a higher digestive power to that required by the Pharmacopœia, sugar of milk should be employed for this purpose.

"A fine, white, or yellowish-white, amorphous powder, or thin, pale yellow or yellowish, transparent or translucent grains or scales, free from any offensive odor, and having a mildly acidulous or slightly alkaline taste, usually followed by a suggestion of bitterness. It slowly attracts moisture when exposed to the air.

"Soluble, or for the most part soluble, in about one hundred parts of water, with more or less opalescence; more soluble in water acidulated with hydrochloric acid; insoluble in alcohol, ether, or chloroform.

"On heating a solution of pepsin in acidulated water to 100° C. (212° F.) it becomes milky, or yields a light, flocculent precipitate, and loses all proteolytic power. In a dry state it can bear this temperature without injury.

"Pepsin usually has a slightly acid reaction. It may be neutral, but should never be alkaline."

Pepsinum Saccharatum, U. S. P.—"Pepsin triturated with milk sugar in such proportion that the resultant saccharated product shall digest three hundred times its own weight of coagulated egg albumen under the United States Pharmacopœia method of valuation for pepsin."

Pepsin of the British Pharmacopœia is of 1–2,500 strength. The United States Pharmacopœia method of valuation (that of the British Pharmacopœia is similar) in brief is this: 0.003 gm. of pepsin is required completely to digest 10 gm. of hard-boiled comminuted egg albumen in 100 c.c. of a 0.2-per-cent. solution of absolute HCl in distilled water, the mixture maintained at a temperature of 100°–104° F. for six hours, and the flask shaken gently every fifteen minutes. At most only a few thin, insoluble flakes should be left. Pepsin fluids must be assayed according to the United States Pharmacopœia method, the conditions prescribed being strictly adhered to, but use being made of a corresponding proportion of the fluid to represent the amount of ferment necessary to digest the 10 gm. of albumen.

Pepsin of the United States Pharmacopœia and British Pharmacopœia requirements is obtained by precipitation, with neutral salts, of the alkalies from purified infusions of the fresh, healthy stomach glands, and the precipitate purified by mechanical means—by reprecipitation and dialysis. By this means mucus is wholly, and non-peptic proteids and peptones well, separated. The *rationale* of the process will appear in the consideration of the nature and behavior of the enzyme.

No official method is given in the United States Pharmacopœia or in the British Pharmacopœia; their standards make obsolete the cruder, earlier forms. It is to be regretted that European standards are so greatly inferior, for a uniform, definite, adequate pharmacopœial standard for pepsin of commerce is absolutely essential. In the past pepsin has been too commonly of insignificant value—even inert; and variable and apparently conflicting results and theories are inevitable when pepsin still means in various countries a product of from 1 to 40 to 1 to 3,000 standard; moreover, there are offered in commerce, in the United States, pepsins of even *stated* digestive value below the obligatory pharmacopœial standard.

Both physiological and chemical data almost irresistibly lead to the conclusion that pepsin is a nucleo-proteid and sharply distinguished from all other forms of proteid by its proteolytic action, exhibited under conditions which are in themselves incapable of effecting these chemical changes without the intervention of the enzyme. The degree of isolation of pepsin is necessarily only to be judged by the energy of the product which is obtained by the exclusion of foreign substances capable of separation and identification by chemical processes and dialysis. The enzyme so far isolated exhibits the characteristic behavior of a nucleo-proteid. It is freely soluble in water, is non-dialyzable, readily precipitated by the neutral salts of the alkalies and by strong alcohol in excess, and is coagulated in solution at 160° F. both in neutral and in acid media; it is destroyed in solution at this temperature (160° F.) which, it is interesting to note, is the coagulating point of albumen and destructive to organized ferments; it is destroyed in alkaline solutions at any temperature; its action is strongly influenced by various reagents which do not in themselves effect any known change in the enzymic substance; and, finally, when once destroyed its vitality cannot be restored by any means whatever. A striking example of its physiological relations is found in its behavior with common salt; the presence of sodium chloride in so small a quantity as one per cent. of the digesting mass completely retards digestion *in vitro*, yet we have the fact that pepsin may be precipitated by means of common salt (in saturated solution), and kept in contact with it for a long time without impairment of its activity.

The most perfectly isolated pepsin yet produced is found to be a nitrogenous body with the chemical constitution of a proteid, and this pepsin-proteid contains phosphorus and iron like other nuclein bodies. The fact, then, that the chemical composition of pepsin remains yet to be absolutely established is of little significance from a therapeutic standpoint, for it imposes, in the light of all the material and important facts known, no limitations upon the complete utilization of the enzyme.

The physiological test for pepsin is as conclusive and reliable as any chemical test by which we establish the presence or identity of any chemical substance. It is by the physiological test that we readily measure the strength of any specimen of pepsin; and it is by it, furthermore, that we have determined the influence of medicinal and food substances upon pepsin, and have gained accurate data as to the conditions which are favorable and unfavorable to its action or destructive to the life of the enzyme. These data clearly reveal that physiological considerations are as conclusive in relation to the enzymes as are chemical reactions, both in theory and in practice, in relation to the use of other agents of the materia medica.

Pepsin behaves as a true ferment whose peculiar form

of energy is capable of liberating latent energy in complex labile substances—the proteids, breaking them down into simpler, more stabile bodies. We have had the statements that pepsin actually loses its activity in this process, and that it remains unaltered. There can be no doubt, however, that pepsin undergoes no change in exerting its energy, for this is readily demonstrated.

A pepsin having been subjected to the usual digestive test—upon acid albumin mixture—may be made repeatedly to exhibit its action upon the addition of fresh volumes of water and albumin and when the requisite percentage of acid is maintained, thus preventing saturation of the digestive fluid with the soluble products formed. In this way the writer has found pepsin to digest several hundred thousand times its own weight of albumen without exhaustion of energy. Interesting as this may be as to the marvellous power of the enzyme, it seems, however, to be without therapeutic bearing, in view of the fact that the gastric juice is normally discharged into the intestine with the completion of the stomach digestion.

Pepsin in the dry form, if non-hygroscopic, retains its vitality for years at ordinary temperature. In solution it may be readily preserved without serious impairment; alcohol and glycerin combined form the best preservatives, from both the medicinal and the pharmaceutical standpoints; for general use, about fifteen per cent. absolute alcohol and glycerin being the amount required. The anhydrous glycerin does not readily take up the enzyme; when diluted with water, to the extent of about forty per cent., it affords a useful vehicle. Elixirs, essences, and glycerites are commonly and very conveniently made with pepsin. There is no pharmacopœial method or standard for these products; they are variable, and distinctly inferior in therapeutic utility to fluids made directly from the fresh stomach.

Chemical preservatives—salicylic acid, boric acid, etc.—are obviously objectionable. Absolute alcohol precipitates pepsin, and by long contact distinctly weakens it; but the presence of alcohol up to about fifteen per cent. exerts no sensible influence upon the ferment, the enzyme being freely extracted by such hydro-alcoholic menstruum. *In vitro* alcohol, when it constitutes ten per cent. of the medium, sensibly affects the *digestive* action of pepsin; and it checks this digestive action, not by altering the ferment, but simply for the reason that alcohol is not a competent medium for the ferment in any particular. The products of enzymic action are insoluble in alcohol and are of lessened solubility in hydro-alcoholic media in direct ratio to increased percentage of alcohol. This, however, concerns digestion *in vitro* solely, for alcohol as present in any proper peptic fluid becomes in this respect a negligible quantity by dilution with gastric content and its free absorption. The inert or feeble nature of many of the vinous and alcoholic preparations has been due to the insignificant amount of pepsin actually contained in them and not simply to their alcohol content. The intimate relation of pepsin to hydrochloric acid has naturally led to the impression that this and other mineral acids may be freely admixed with the ferment; but this is a serious error. The acid of the gastric juice is bound up in a peculiar manner with the proteids, and thus the enzyme seems to be protected from the acid, whereas pepsin in solution with pure water and the normal content of absolute HCl (0.2 per cent.) rapidly deteriorates at ordinary temperature. This constitutes a striking evidence of the fact that a solution of pepsin and water and HCl is not gastric juice; it represents the proteolytic ferment, and exhibits absolutely the proteolytic action only of the gastric juice. Other mineral acids are distinctly injurious to the ferment in any fluid form. It is not possible to mix a mineral acid in medicinal quantity with pepsin in a fluid mixture of convenient volume of dosage without distinctly injuring the ferment even for extemporaneous use; while combined in a percentage much above that of the gastric juice content, such mixtures are distinctly incompatible with the normal activity of the ferment and unsuited for pharmaceutical products. For instance, if we take five minims as a moderate dose of official dilute HCl, this in two fluidrachms would yield an acidity of 0.42 absolute HCl, which is twice the acidity of normal gastric juice and fatal to the enzyme.

Pepsin fluids should have an acid reaction; but when acids *per se* are indicated medicinally, it is the best practice to exhibit them separately by such vehicle and means as are most desirable in conjunction with the pepsin preparation. If the preparation has an alkaline reaction, this is conclusive evidence of its inertness.

Pepsin is incompatible with bismuth ammonio-citrate in solution. If the mixture has a neutral or an alkaline reaction, the ferment cannot retain its activity; on the other hand, if it is acid, it is impossible to maintain the bismuth in solution. Owing to the unstable and insoluble nature of the salt, its solution is usually effected by the addition of ammonia, which is obviously incompatible with pepsin. The therapeutic value of elixirs of pepsin, bismuth, and strychnine necessarily cannot be attributed in any degree to pepsin; devitalized pepsin cannot in any way add to the value of a medicinal compound.

Pepsin and pancreatin are incompatible in solution, for the reason that if the menstruum be of such acid nature as to preserve the pepsin, the pancreatic enzyme will be in time destroyed; while if it is neutral or feebly alkaline, the pepsin will be destroyed. Acid-pepsin fluids are unsuitable for the admixture of all ferments except the milk-curdling; the pepsin will be the only enzyme of all those originally combined which will retain its activity. Mixtures of the ferments in solution are readily subject to recognized tests for the presence of any one of the ferments. If a fresh and feebly acid infusion of the stomach, or solution of pepsin, be mixed with an aqueous infusion of the pancreas, each one of the ferments contained in this mixture may be immediately made to exert its peculiar action under the proper conditions; the mixture will exhibit the digestive action of pepsin, of trypsin, and of diastase. But upon keeping this mixed ferment solution at ordinary room temperature for a few weeks, it will be found upon systematic assay to have gradually and rapidly deteriorated in respect to one or another of its ferments.

The fact that a number of ferments are mixed in any fluid does not in the least interfere with the method of assay for testing or determining the presence of any one or of each separate ferment in the fluid mixture. When it is desired to combine gastric and pancreatic ferments in solution, they are best directed in extemporaneous mixture of preparations which have been obtained directly from the stomach and the pancreas gland, and thus they will maintain their individual action for such length of time as will ordinarily be required by the patient.

The therapeutic use of pepsin is prejudiced and complicated by the prevalence, in the past, of inefficient products and incompatible combinations, a condition which does not exist concerning any other agent or class of agents of the materia medica, owing to the fact that with the definite and standardized chemicals and galenical products there has been presented no such obstacle in establishing therapeutic action and scientific dosage. The increasing knowledge and application of physiological chemistry in therapeutics, and the accumulation of laboratory and clinical observations with regard to the action of animal gastric juice, have strongly confirmed its rational and obvious utility and promise, and have advanced its repute and use as a therapeutic agent.

Pepsin exhibited in adequate doses aids gastric digestion, with effects apparent in the relief of various dyspeptic symptoms and in the promotion of nutrition; it affords a rational remedy to which the physician may have recourse in cases of feeble and readily disturbed digestion. The beneficial effects of pepsin are not restricted alone to the improvement of gastric disorders; there is abundant evidence that each step in the chain of digestive action is of essential importance, and defective stomach digestion cannot but influence the entire digestive process.

The pancreatic ferments attack with great facility the soft and partially converted proteids and starches in the form in which they normally reach the intestinal tract, breaking them down into their most soluble and diffusible forms, and the development of the latent pancreas enzymes waits upon the influence of constituents of normal gastric juice. Coagulated protein food in masses is but very slightly attacked by pancreas juice in contrast with peptic action, and thus the complete conversion of food is absolutely dependent upon the interaction of both gastric and intestinal digestion. Disorders even of the intestinal tract are frequently benefited by the administration of pepsin. Pepsin in doses so small as to seem a slight factor in the physiological process, and administered either just before or immediately after eating, produces results which can be attributed only to the theory advanced that it imparts an impetus to peptic secretion and action. Pepsin is used to promote the toleration of drugs which impair the appetite and disturb digestion. For all these purposes the gastric juice, extracted directly from the fresh stomach in proper pharmaceutical form, is found most generally useful. This preparation renders available at once all the properties of the gastric juice, both its enzymes (the peptic and milk-curdling) and its acid in proteid combination—the entire organic and inorganic content in natural association. These enzymes are thus less susceptible to unfavorable influence than is the precipitated ferment.

Pepsin is given in scales, powder, tablets, and capsules, ordinarily in doses of from one to five grains; the scales are readily soluble in water—plain or with acid; the glycerite, especially the glycerin extract from the stomach, is useful, and if properly prepared is far more agreeable than the scale itself taken in solution. The essence prepared from the gastric juice is the most efficient and agreeable preparation, and its grateful qualities enhance the effect of the digestive principles contained therein. The desired dose of drug, for instance sodium salicylate or iodide of potassium, is prescribed in the proportion of, say, five grains to each teaspoonful of the essence of pepsin, and this added to two or three tablespoonfuls of warm milk gives instantly a firm curd. The milk may be previously sweetened or flavored if desired, the object being to present the drug in a small bulk for convenience; even this serves well to disguise the medicine.

When pepsin is given simply to promote digestion, it should never be administered in a disagreeable form, and when given to facilitate the exhibition and therapeutic action of disagreeable drugs, the essence is not only valuable as a vehicle, but should be given immediately after the drug if it is desired to obtain its best effect.

The essence of pepsin is much used in combination with savory, soluble, and diffusible food products, the prepared peptonized foods, and it should be mixed in about equal quantities therewith; this combination proves of peculiar value in acute forms of indigestion and intolerance of food; in seasickness, for instance, it is especially useful. Essence of pepsin is also much used in combination with pure phenol, which is thus well masked and well borne, and this mixture, which is both antiseptic and sedative to an irritable gastric mucous membrane, does not in medicinal proportion unfavorably influence the gastric enzymes.

The gastric juice essence is more especially found serviceable as a drug vehicle, and in conjunction with it maximum doses of mercurials, iodides, salicylates, etc., are peculiarly well tolerated. It is also valuable for the production of junket—a jelly-like, diffusible form of pure milk—which is also a carrier of drugs which blend with it and thus lose much of their disagreeable taste and effect. Junket affords an agreeable and wholesome variety of food, and is serviceable in convalescence where liquid foods have become distasteful and are no longer required. It is made as follows:

Junket.—Into a clean saucepan put one-half pint of fresh, cool milk, heat it lukewarm (not over 100° F.); then add one teaspoonful of essence of pepsin, and stir just enough to mix; divide quickly into small cups or glasses and let stand until firmly jellied, when the junket is ready for use, just as it is, or with sugar; it may be placed on ice and taken cold.

Whey.—After preparing the junket by the above method, let it stand until firmly jellied, then beat with a fork until it is finely divided; now strain and the whey (liquid part) is ready for use; keep in a bottle near ice.

Pepsin digestion has long been observed to effect the solution of dead tissue, pus, necrosed bone, etc. The availability of the gastric juice in an active, sterile, and stable extract of great potency, has recently led to its application as a surgical solvent in the bladder, urethra, eye, ear, nose, and throat, and in pus cases in general—sores, abscesses, carbuncles, gangrene, leg ulcers, etc. Gastric juice is thus found to possess peculiar and valuable properties as a solvent, healing, antiseptic, deodorizing, and sedative agent. It is painless in its action and incapable of attacking normal tissue, and has caused a speedy cure in cases which were so aggravated as to have resisted other treatment, thus rendering surgical interference unnecessary. In genito-urinary diseases it promises, from the most conservative estimate of the clinical trial which it has already received, to afford a remedy of great importance.

Benjamin T. Fairchild.

PEPTONURIA. See *Urine, etc.*

PERFORATING ULCER OF THE FOOT.—This is a rare affection, caused by pressure or injury where there is a degenerated nerve supply. It is found in leprosy, locomotor ataxia, lues, and alcoholic and diabetic neuritis. The most common location is where there is great pressure, as over the metatarso-phalangeal articulation of the great or little toe, or over the ball of the toes. Occasionally there are several lesions existing at the same time in one or both feet. A similar condition may also occur on the hands.

The process is very slow. It begins as a thickening of the skin resembling a corn, under which suppuration occurs; and later, when the horny plug is cast off, an ulcer is left. The destructive process extends downward until it reaches the bone, which may also become affected. The condition now is more that of a sinus than of an ulcer. The skin surrounding the opening is usually much thickened, and there may be granulations at the orifice. The diseased parts are generally painless and the neighboring parts are usually anæsthetic. Distortion of the toes, as well as trophic changes in the nails, may occur later; they are usually accompanied by an increased growth of hair, pigmentation, and hyperidrosis. The patients frequently complain of cold feet and neuralgic pains.

The prognosis is unfavorable, even if the lesions should heal, on account of the liability to recurrence, which in turn is due to permanent nerve lesions.

Perforating ulcer has to be differentiated only from a suppurating corn, which latter is painful and is accompanied by abnormal sensitiveness of the surrounding skin. In the case of a suppurating corn the results of surgical treatment are always satisfactory.

Prolonged rest will occasionally lead to healing of the lesion in the early stages, but exercise will cause the sore to recur. Packing the sinus with lint wet with a saturated solution of salicylic acid in glycerin, and the employment of mechanical devices to prevent pressure will frequently produce a temporary cure. Free opening of the sinus or stretching of the nerves which supply the part has been followed by good results in some cases. In the later stages excision of the ulcer is useless and amputation of the foot is necessary. Even then the ulcer may recur in the stump, unless the limb is removed at a point far from the lesion and above the line of anæsthesia.

Howard Morrow.

PERICARDIUM, DISEASES OF THE.—HISTORY.—Anatomical alterations in the pericardium were known long before diseases of the heart proper received careful