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Enzymes and Other Proteins

ENZYMES

Enzymes are organic catalysts produced by living organisms. They make possible the many complex chemical reactions that make up life processes. Although produced by living organisms, enzymes are lifeless. When isolated, they still exert their characteristic catalytic effect. Although their chemical composition varies, they do exhibit several common properties: (1) enzymes are colloids and are soluble in water and dilute alcohol but are precipitated by concentrated alcohol; (2) most enzymes act best at temperatures between 35 and 40° C; temperatures above 65° C, especially in the presence of moisture, usually completely destroy them, whereas their activity is negligible at 0° C; (3) certain heavy metals, formaldehyde, and free iodine retard the enzyme's activity. Their activity is markedly affected by the pH of the medium in which they act or by the presence of other substances in this medium. They are usually highly selective in their action.

The enzymes are proteins that range in molecular weight from about 13,000 to as much as 840,000. At present they are classified according to their action by a complex system established by the Commission on Enzymes of the International Union of Biochemistry. Six major classes are recognized; each has 4 to 13 subclasses, and each enzyme is assigned a systematic code number (E.C.) composed of 4 digits. The major classes in this system are:

1. **Oxidoreductases**—catalyzing oxidoreductions between 2 substances.
2. **Transferases**—catalyzing a transfer of a group, other than hydrogen, between a pair of substrates.
3. **Hydrolases**—catalyzing hydrolysis of ester, ether, peptide, glycosyl, acid-anhydride, C-C, C-halide, or P-N bonds.
4. **Lyases**—catalyzing removal of groups from substrates by mechanisms other than hydrolysis, leaving double bonds.
5. **Isomerases**—catalyzing interconversion of optic, geometric, or positional isomers.
6. **Ligases**—catalyzing linkage of 2 compounds coupled to the breaking of a pyrophosphate bond in ATP or a similar compound.

Because the nomenclature of enzymes was rather well established prior to the promulgation of this system, the well-known trivial names are still ordinarily employed in the pharmaceutic literature. Those encountered with some frequency are:

1. **Esterases,** including lipase, phospholipase, acetylcholinesterase, and others.

2. **Carbohydrases,** including diastase, lactase, maltase, invertase, cellulase, hyaluronidase, glucuronidase, lysozyme, and others.
3. **Nucleases,** including ribonuclease, desoxyribonuclease, nucleophosphatase, and others.
4. **Nuclein deaminases,** including adenase, adenosine deaminase, and others.
5. **Amidases,** including arginase, urease, and others.
6. **Proteolytic enzymes,** including pepsin, trypsin, chymotrypsin, papain, fibrinolysin, streptokinase, urokinase, and others.

Enzymes often occur in combination with inorganic or organic substances that have an important part in the catalytic action. If these are nonprotein organic compounds, they are known as **coenzymes.** If they are inorganic ions, they are referred to as **activators.** Coenzymes are integral components of a large number of enzyme systems. Several vitamins (thiamine, riboflavin, nicotinic acid) are recognized as having a coenzymatic function.

Because enzymes may be recovered from plant and animal cells and because many have been purified, they are utilized as therapeutic agents in addition to their use as controlling factors in certain chemical reactions in industry. Pepsin, pancreatin, and papain are employed therapeutically as digestants; hyaluronidase facilitates the diffusion of injected fluids; streptokinase and streptodornase dissolve clotted blood and purulent accumulations; zymase and rennin are used extensively in the fermentation and cheese industries; and penicillinase inactivates the various penicillins.

Although the terminology is variable, the names used to designate enzymes usually end in *-ase* or *-in*. Some of the more common enzymes are listed in the following classification.

I. The Amylolytic Enzymes or Carbohydrases

Diastase and amylase are terms applied to 2 well-known amylolytic enzymes. Salivary diastase or **ptyalin** and pancreatic diastase or **amylopsin** are found in the digestive tract of animals; they are sometimes called "animal diastase." **Malt diastase** is formed during the germination of barley grains and converts starch into maltose. It is most active in solutions that are approximately neutral; acidity of pH 4 destroys the enzyme.

Invertase or sucrase is found in yeast and in the intestinal juices. It brings about the hydrolysis of sucrose into glucose and fructose. **Maltase,** which causes the conversion of maltose into glucose, is also found in yeast and the intestinal juices.

Zymase is a fermenting enzyme causing the conversion of monosaccharides (glucose, fructose) into alcohol and carbon dioxide.

Emulsin is an enzyme found in almonds. It causes the hydrolysis of β-glucosides; thus, amygdalin is hydrolyzed into glucose, benzaldehyde, and hydrogen cyanide.

Myrosin is found in white and black mustard; it hydrolyzes sinalbin, sinigrin, and other glycosides.

II. The Esterases

Lipase is a lipolytic enzyme widely distributed in the animal and vegetable kingdoms. It is found in the pancreatic juice of animals and in oily seeds. Lipase causes the hydrolysis of fats into glycerin and fatty acids.

Pectase splits pectin into pectic acid and methyl alcohol.

Steapsin is a lipolytic enzyme capable of digesting dietary fat.

Urease is obtained from soybeans and is used as a laboratory reagent for converting urea to ammonia.

III. The Proteolytic Enzymes

Pepsin is a proteolytic enzyme found in the gastric juice. It is most active at a pH of about 1.8, but in neutral or alkaline media, pepsin is entirely inactive. It converts proteins into proteoses and peptones.

Trypsin is formed when the proenzyme, trypsinogen, is acted on by the enterokinase of the intestinal juices. Trypsin is a proteolytic enzyme that is considerably more active than pepsin, converting proteoses and peptones into polypeptides and amino acids. It acts best in an alkaline medium of about pH 8 and may thus be distinguished from pepsin, which acts only in acid media.

Erepsin is a proteolytic enzyme also found in the intestinal juices. It converts proteoses and peptones into amino acids.

Rennin is a coagulating enzyme present in the mucous membrane of the stomach of mammals. It curdles the soluble casein of milk.

Papain is a mixture of active proteolytic enzymes found in the unripe fruit of the papaya tree. It is a meat tenderizer.

The rationale for oral or parenteral use of proteolytic enzymes in the treatment of traumatically induced inflammation and edema of soft tissues is questionable. Evidence of therapeutic usefulness in such conditions is based solely on the subjective interpretation of results and is, at best, inconclusive.

IV. The Oxidizing Enzymes

Peroxidases are widely distributed in plants. They bring about the oxidation reactions that cause the discoloration of bruised fruits.

Thrombin converts the fibrinogen of the circulating blood into the insoluble fibrin of the blood clot.

Zymase, although splitting monosaccharides, is essentially an oxidizing enzyme because the monosaccharide is split by oxidation.

Malt Extract

Barley is the dried grain of one or more varieties of *Hordeum vulgare* Linné (Fam. Gramineae). Barley is grown throughout the world wherever the climate is favorable.

Malt or malted barley is dried, artificially germinated barley grain. To prepare malt, heaps of barley grain are kept wet with water in a warm room and allowed to germinate until the caulicle protrudes. The grain is then quickly dried. The enzyme diastase in the moist warm grains converts the starch to maltose, thereby stimulating the embryo to growth. The embryo is killed when the grain is dried.

Dry malt resembles barley but is more crisp, has an agreeable odor, and has a sweet taste. It contains 50 to 70% of the sugar, maltose; 2 to 15% of dextrins; 8% of proteins; diastase; and a peptase enzyme.

Malt is used extensively in the brewing and alcohol industries.

Malt extract is the product obtained by extracting malt, the partially and artificially germinated grain of one or more varieties of *Hordeum vulgare*. The malt is infused with water at 60° C, and the expressed liquid is concentrated at a temperature not exceeding 60° C, preferably under reduced pressure.

Malt extract may be mixed with 10%, by weight, of glycerin. It contains dextrin, maltose, a small amount of glucose, and amylolytic enzymes. It can convert not less than 5 times its weight of starch into water-soluble sugars.

USES AND DOSE. Malt extract is used as an easily digested nutritive and as an aid in digesting starch. The usual dose is 15 g. Many commercial extracts of malt do not contain diastase, which is destroyed by the heat used for their sterilization. Such extracts should not be confused with this product. They are used as bulk-producing laxatives. An example is Maltsupex®.

Diastase is a yellowish white, amorphous powder obtained from an infusion

of malt. It can convert 50 times its weight of potato starch into sugars.

Lactase is an enzyme that hydrolyzes lactose to galactose and glucose. It is obtained commercially from the yeast, *Saccharomyces lactis*, and is used as LactAid® Powder to help patients with lactose intolerance to digest the lactose in milk or milk products.

Pepsin

Pepsin is a substance containing a proteolytic enzyme obtained from the glandular layer of the fresh stomach of the hog, *Sus scrofa* Linné var. *domesticus* Gray (Fam. Suidae). The generic name *Sus* is from the Greek *Us*, meaning hog; *scrofa* is Latin and means breeding sow; and *domesticus* is Latin and means the household.

Pepsin is prepared by digesting the minced stomach linings with hydrochloric acid. This solution is clarified, partially evaporated, dialyzed, concentrated, and either poured on glass plates to dry, thus forming **scale pepsin,** or carefully evaporated in a vacuum, forming **spongy pepsin.**

Pepsin occurs as lustrous, transparent, or translucent scales, as granular or spongy masses ranging in color from light yellow to light brown, or as fine white or cream-colored amorphous powder. It is free from offensive odor and has a slightly acid or saline taste.

Pepsin digests not less than 3000 and not more than 3500 times its weight of coagulated egg albumin. A pepsin of higher digestive power may be reduced to the standard by admixture with a pepsin of lower power or with lactose. NOTE: Pepsin produced commercially, especially spongy pepsin, often is 4 to 5 times as active as that used medicinally.

Pepsin is administered to assist gastric digestion. It is a proteolytic enzyme and should preferably be given after meals and followed by a dose of hydrochloric acid. The usual dose is 500 mg. It is often combined with pancreatin in product formulations. Pepsin has a long history of use in medicine, but its actual beneficial contribution is poorly documented.

Pancreatin

Pancreatin is a substance containing enzymes, principally amylase, lipase, and protease. It is obtained from the pancreas of the hog, *Sus scrofa* Linné var. *domesticus* Gray (Fam. Suidae), or of the ox, *Bos taurus* Linné (Fam. Bovidae). The pancreas is a gland that lies directly inside the posterior wall of the abdomen. The fresh glands are minced and extracted by methods similar to those employed in the manufacture of pepsin.

Pancreatin is a cream-colored amorphous powder with a faint, characteristic, but not offensive, odor. Its greatest activity is in neutral or faintly alkaline solution. More than traces of mineral acids or large amounts of alkali hydroxides render pancreatin inert, and an excess of alkali carbonates inhibits its action.

Pancreatin contains, in each mg, not less than 25 USP units of amylase activity, not less than 2 USP units of lipase activity, and not less than 25 USP units of protease activity. Pancreatin of a higher digestive power may be labeled to indicate its strength in whole-number multiples of the 3 minimum activities or may be diluted by appropriate admixture to conform to aforementioned specifications. One USP unit of amylase activity is contained in the amount of pancreatin that digests 1 mg of dry USP Potato Starch Reference Standard, 1 USP unit of lipase activity liberates 1 μEq of acid per minute at a pH of 9 and at 37° C, and 1 USP unit of protease activity digests 1 mg of casein, all under specified conditions.

Pancreatin is a digestive aid and is also used in the preparation of predigested foods for invalids. Enteric-coated granules of pancreatin have been used to treat infants with celiac disease and related pancreatic deficiencies. The usual dose is 325 mg to 1 g as tablets, capsules, or granules.

PROPRIETARY PRODUCTS. Elzyme®, Panteric®, Viokase®. Products containing both

pepsin and pancreatin in combination with bile salts include Digestozyme®, Donnazyme®, Enzobile®, Entozyme®, Gastroenterase®, Gourmase®, and Nu'Leven®. Bilogen®, Co-Bile®, Digestalin®, Digestex®, Digolase®, Enzymet®, Enzypan®, and Zypan® are related products.

Pancrelipase

Pancrelipase is essentially a more concentrated form of pancreatin. In each mg it contains not less than 24 USP units of lipase activity, 100 USP units of amylase activity, and 100 USP units of protease activity. Thus the lipase activity is increased 12-fold, but the activity of amylase and protease only 4-fold when compared with pancreatin.

Employed as a digestive aid, pancrelipase increases the intestinal absorption of fat, thus aiding in the control of steatorrhea. It is available in the form of capsules, powder packets, and tablets. The usual dose range is 8000 to 24,000 USP units of lipolytic activity prior to each meal or snack, to be determined by the practitioner according to the needs of the patient suffering from pancreatic insufficiency.

PROPRIETARY PRODUCTS. Accelerase®, Cotazym®, Ilozyme®, Ku-Zyme HP®, Pancrease®, Viokase®.

Papain

Papain is the dried and purified latex of the fruit of *Carica papaya* Linné (Fam. Caricaceae). The papaya tree is indigenous to tropical America and is cultivated in Sri Lanka, Tanzania, Hawaii, and Florida. It attains a height of about 5 to 6 meters. The fruit (Fig. 10–1) grows to a length of about 30 cm and a weight of 5 kg. The epicarp adheres to the orange-colored, fleshy sarcocarp, which surrounds the central cavity. This cavity contains a mass of nearly black seeds.

The full-grown but unripe fruit is subjected to shallow incisions on the 4 sides. The latex flows freely for a few seconds but soon coagulates. After collection, the coagulated lumps are shredded and dried by the sun or by the use of artificial heat, the latter method yielding the better grade of crude papain. Incisions and collections are made at weekly intervals as long as the fruit exudes the latex. The crude papain is purified by dissolving in water and precipitating with alcohol. Papain has been referred to as "vegetable pepsin" because it contains enzymes somewhat similar to pepsin; however, unlike pepsin, papain acts in acid, neutral, or alkaline media.

Papain contains several enzymes: one or more proteolytic enzymes, among which is peptidase I, capable of converting proteins into dipeptides and polypeptides; a renninlike, coagulating enzyme that acts on the casein of milk; an amylolytic enzyme; a clotting enzyme similar to pectase; and an enzyme that has a feeble activity on fats. It is quite apparent that more than one proteolytic enzyme is present because a single sample of papain yields variable results, depending on the protein used. Although differing in strength in accordance with the method of manufacture, papain can digest about 35 times its own weight of lean meat. For this reason, it is used to tenderize meats. The best grade of papain digests 300 times its own weight of egg albumin.

Papain is used as a digestant for proteins because it has an action much like that of pepsin. It is employed to relieve the symptoms of episiotomy (surgical incision of the vulva for obstetric purposes). Another use of the enzyme is as an ingredient in cleansing solutions for soft contact lenses. In the meat packing industry, papain is used extensively for tenderizing beef.

PROPRIETARY PRODUCTS. Panafil®, Papase®, and Softlens Enzymatic Contact Lens Cleaner®.

Chymopapain

Chymopapain is a nonpyrogenic proteolytic enzyme obtained from the latex of *Carica papaya* Linné (Fam. Caricaceae). It is a sulfhydryl enzyme similar to papain with respect to substrate specificities but differ-

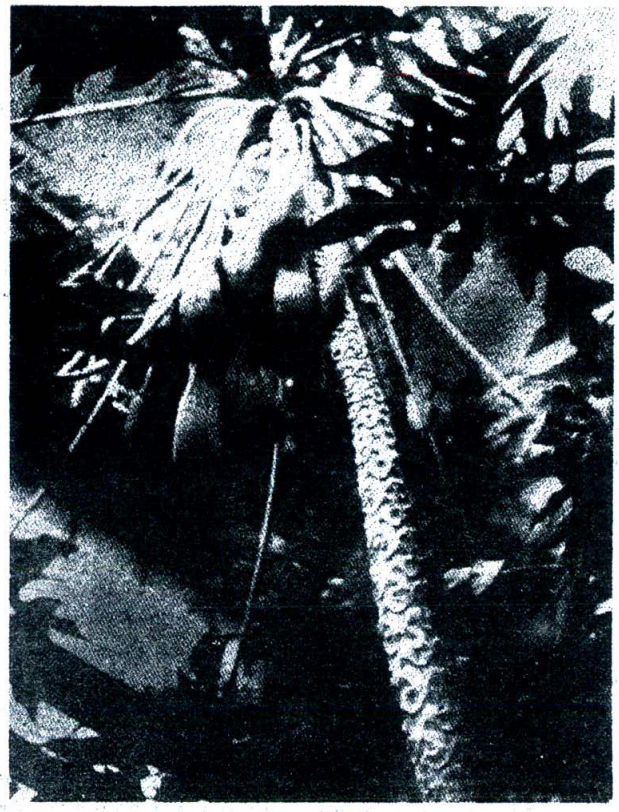


Fig. 10–1. Fruits of *Carica papaya*.

ing in electrophoretic mobility, stability, and solubility.

Employed in the treatment of herniated lumbar intervertebral discs, chymopapain is injected into the nucleus pulposus to hydrolyze the noncollagenous polypeptides or proteins that maintain the tertiary structure of the chondromucoprotein. This relieves the compressive symptoms of lower back pain by lessening osmotic activity and thereby decreasing fluid absorption and reducing intradiscal pressure. About 75% of the patients so treated respond favorably.

The unit of chymopapain activity is the nanoKatal (nKat), and 1 mg of the enzyme contains at least 0.52 nKat units. The dosage is 2 to 5 nKat units per disc or a volume of injection of 1 to 2 ml. The maximum dose in a single patient requiring treatment of multiple discs is 10 nKat units. Chymopapain is marketed in 5-ml sterile vials containing 10 to 12.5 nKat units. This is equivalent to 2 or 2.5 units per ml following reconstitution.

PROPRIETARY PRODUCTS. Chymodiactin®, Discase®.

Bromelains

Bromelains, bromelain, or bromelin is a mixture of protein-digesting and milk-clotting enzymes obtained from the juice of the pineapple plant, *Ananas comosus* (Linné) Merr. (Fam. Bromeliaceae). Although this enzyme can appear in the juice of the fruit, it can also occur in the stem of the plant. It differs from papain because it is obtained from both the ripe and unripe fruits.

Bromelain is used as adjunctive therapy to reduce inflammation and edema and to accelerate tissue repair, especially follow-

ing episiotomy. Its effectiveness in such conditions is apparently owing to depolymerization and permeability modifications that they induce following oral administration. Bromelains are also employed in the production of protein hydrolysates, in tenderizing meats, and in the leather industry.

PRESCRIPTION PRODUCT. Ananase®.

Trypsin

Crystallized trypsin is a proteolytic enzyme crystallized from an extract of the pancreas gland of the ox, *Bos taurus* Linné (Fam. Bovidae). When assayed as directed, it contains not less than 2500 USP trypsin units in each mg. It occurs as a white to yellowish white, odorless, crystalline or amorphous powder. The assay involves a spectrophotometric comparison of the solution to be tested to known solutions of measured USP trypsin crystallized reference standard. Similar to other enzymes, crystallized trypsin is stable in the dry state but rapidly deteriorates in solution form. Thus, it should be stored in tight containers away from excessive heat.

Crystallized trypsin is a proteolytic enzyme. It has been employed orally, topically, or by inhalation or local injection for debridement of necrotic and pyogenic surface lesions. Proof of efficacy of oral and parenteral administration of proteolytic enzymes in such conditions is lacking. The current use of trypsin is primarily topical by aerosol application for wound and ulcer cleansing.

PRESCRIPTION PRODUCT. Granulex®.

Chymotrypsin

Chymotrypsin is a proteolytic enzyme crystallized from an extract of the pancreas gland of the ox, *Bos taurus* Linné (Fam. Bovidae). It contains not less than 1000 USP chymotrypsin units in each mg. The enzyme occurs as a white to yellowish white, odorless, crystalline or amorphous powder. Chymotrypsin is available as **chymotrypsin for ophthalmic solution.**

This proteolytic enzyme is administered in solution to the posterior chamber of the eye, under the iris, to achieve zonal lysis. One to two ml of a solution containing 75 to 150 units per ml are ordinarily applied. Products, usually in combination with trypsin, are available for oral use.

PRESCRIPTION PRODUCTS. Alpha Chymar®, Avazyme®, Catarase®, Zolyse®.

COMBINATION PRODUCTS. Chymoral®, Orenzyme®.

Hyaluronidase

Hyaluronidase for injection is a sterile, dry, soluble, enzyme product prepared from mammalian testes and capable of hydrolyzing mucopolysaccharides of the type of hyaluronic acid. Its potency is expressed in USP hyaluronidase units. Hyaluronidase for injection contains not more than 0.25 μg of tyrosine for each USP hyaluronidase unit.

Hyaluronidase is a mucolytic enzyme capable of depolymerizing and catalyzing hyaluronic acid and similar hexosamine-containing polysaccharides. It is also a spreading and a diffusing factor. It occurs in human testes, in various bacterial cultures as a metabolic product, in heads of leeches, and in snake venoms. Because of its action on hyaluronic acid, this enzyme promotes diffusion and hastens absorption of subcutaneous infusions.

Hyaluronidase for injection is a spreading agent. The usual dose, hypodermoclysis, is 150 USP units.

PRESCRIPTION PRODUCTS. Alidase®, Wydase®.

Streptokinase

Streptokinase is a purified bacterial protein elaborated by group C β-hemolytic streptococci. It is supplied as a lyophilized powder. The compound acts to convert plasminogen to the proteolytic enzyme plasmin. Plasmin degrades not only fibrin clots but also fibrinogen and other plasma proteins.

Use of streptokinase is indicated in the treatment of pulmonary embolism, deep

vein thrombosis, arterial thrombosis and embolism, arteriovenous cannula occlusion, and coronary artery thrombosis. At present, it is particularly widely used for the last condition, often producing a prompt recanalization of the involved vessel. The route of administration, dosage, and duration of treatment vary for each of the above conditions. Streptokinase is marketed in sterile vials containing 250,000 to 750,000 IU.

PRESCRIPTION PRODUCTS. Kabikinase®, Streptase®.

Urokinase

Urokinase is an enzyme isolated from human urine or obtained from human kidney cells by tissue culture techniques. There are two forms; both have similar clinical effects, but they differ in molecular weight. The product now available commercially derives from tissue culture and is primarily the low-molecular-weight form. It is marketed as a sterile, lyophilized white powder.

The enzyme acts on the endogenous fibrinolytic system, converting plasminogen to the enzyme plasmin. Plasmin degrades fibrin clots as well as fibrinogen and other plasma proteins. Use of urokinase is indicated in the treatment of pulmonary embolism, coronary artery thrombosis, and in restoring the patency of intravenous catheters. It appears to have a reduced probability of serious allergic reactions, presumably owing to its human origin but should be used with appropriate caution. The usual dosage regimen is a priming dose followed by administration of 4,400 units per kg of body weight per hour for 12 hours by intravenous infusion.

PRESCRIPTION PRODUCT. Abbokinase®.

Fibrinolysin and Desoxyribonuclease

Fibrinolysin is in the blood serum as a protease and in plasma as the inactive precursor, profibrinolysin (or plasminogen). It is prepared commercially by activating a human blood plasma fraction with streptokinase. In the dried form, fibrinolysin retains its proteolytic activity almost indefinitely; however, in solution form, it rapidly deteriorates. Its enzymatic activity is lost completely when it is exposed to room temperature for 6 to 8 hours. It can attack the protein portions of dead tissues, exudates, and blood clots found in wounds, ulcers, and burns. Fibrinolysin is used primarily in the treatment of blood clots within the cardiovascular system, exclusive of thrombi of the coronary and cerebral arteries.

Desoxyribonuclease or deoxyribonuclease is a nucleolytic enzyme that is obtained in a highly purified state from pancreatic glands of bovine origin. Like fibrinolysin, it is stable in dry form but rapidly loses its activity in solution form. It can catalyze cleavage of the giant molecules of desoxyribonucleic acid into numerous fragments of smaller size (polynucleotides); thus, it acts against devitalized tissues in purulent states. It is available as a combination product with bovine fibrinolysin.

COMBINATION PRODUCT. Elase®.

Sutilains

Sutilains is a substance containing proteolytic enzymes derived from the bacterium *Bacillus subtilis*. It contains not less than 2.5 million USP casein units of proteolytic activity per g. This cream-colored powder is applied topically, in ointment form, 2 to 4 times daily, for wound debridement.

PRESCRIPTION PRODUCT. Travase® Ointment contains 82,000 USP casein units of proteolytic activity per g.

Collagenase

Collagenase is an enzyme preparation obtained from fermentative cultures of *Clostridium histolyticum*. It cleaves collagen and is used topically to debride dermal ulcers and severely burned areas. Care should be exercised to avoid heavy metal inactivation of the enzyme; Burow's solu-

tion can be used to stop the enzyme's action if the risk of bacteremia develops. Available ointments contain 250 units of collagenase activity per g.

PROPRIETARY PRODUCTS. Collagenase ABC®, Santyl®.

L-Asparaginase

L-Asparaginase, an enzyme obtained from cultures of certain strains of *Escherichia coli,* induces hematologic and clinical remissions of short duration in a significant percentage of children with acute leukemia. The antitumor effect may be attributed to degradation by the enzyme of circulating L-asparagine, which results in the death of cells that require exogenous sources of this amino acid for survival. The notable absence of toxicity to normal marrow elements suggests that the effectiveness of the drug is related to a difference in the requirement for L-asparagine between normal cells and some neoplastic cells.

A number of serious adverse reactions are noted with asparaginase, including allergic reactions and fatal anaphylaxis. It is used primarily in combination with other chemotherapeutic agents, such as prednisone and vincristine. Administration is intravenous, usually 1,000 units per kg of body weight daily, or intramuscular, 6,000 units per square meter of body surface at 3-day intervals.

PRESCRIPTION PRODUCT. Elspar®.

OTHER PROTEINS

Proteins are nitrogenous organic substances produced by and associated with living matter. They occur in both plants and animals; those from plants are more easily isolated in crystalline form. Plants usually store proteins in the form of aleurone grains. In animals, proteins occur as living matter, thus making them difficult to obtain in the individual state.

Proteins may be classified into 3 groups: **simple, conjugated,** and **derived.** The simple proteins hydrolyze entirely into amino acids; the conjugated proteins are combinations of a protein and a nonprotein group (the latter is called the prosthetic group); and the derived proteins are degradation products of the proteins. Each of these groups has several subdivisions.

Because they are present in all living matter, proteins are of great importance in biochemistry. They form an important class of food and are equally as essential as carbohydrates and fats. Meat, fish, and eggs are important sources of animal protein foods. Cereal grains, particularly wheat and soybeans, are sources of plant protein foods.

Although proteins are important in metabolism, relatively few isolated proteins are employed as therapeutic agents. Whole glandular products, oil-bearing plant seeds, antitoxins, serums, and globulins contain proteins in combination with other biochemical substances—all these substances possess therapeutic activity, but they are classified in other chapters of the text. Allergens are usually proteinaceous by nature; however, carbohydrates and fats may also produce allergic reactions. Allergens are described in Chapter 14.

Certain proteins are highly poisonous: the plant lectins (formerly known as toxalbumins), **ricin** from castor beans, **robin** from locust bark, and **abrin** from jequirity seeds. Among the poisonous animal proteins are hemolysins from salamanders (*Triturus* spp.) and the various toxins, **neurotoxoids,** from snake venom (see page 408).

The following drugs are composed of proteins, modified proteins, and amino acids; their therapeutic applications are extremely varied. They are grouped together according to homogeneity of origin rather than similarity of function.

Gelatin

Gelatin is a product obtained by the partial hydrolysis of collagen derived from the skin, white connective tissue, and bones of

animals. Commercially, gelatin is prepared from the suitable by-products of slaughtered cattle, sheep, and hogs. Bones are first decalcified by treatment with hydrochloric acid. The materials are extracted with boiling water and steam under pressure until the collagen is hydrolyzed. The solution is then filtered by electro-osmosis, concentrated under reduced pressure, allowed to gel, and rapidly dried on netting in currents of warm air.

Gelatin occurs in sheets, flakes, shreds, or as a coarse or fine powder. It is faintly yellow or amber and has a slight, characteristic odor and taste. When dry, gelatin is stable in the air, but when moist or in solution, it is subject to bacterial decomposition. Gelatin is insoluble in cold water but swells and softens when immersed in cold water, gradually absorbing from 5 to 10 times its weight of water. It is soluble in hot water and insoluble in most immiscible solutions and in volatile and fixed oils.

Commercially, gelatin is available as 2 types: A and B. Type A exhibits an isoelectric point between pH 7 and 9 and is incompatible with anionic compounds such as acacia, tragacanth, and agar. Type B, on the other hand, should be used when such mixtures are desired because it exhibits an isoelectric point between pH 4.7 and 5.

If gelatin is intended for use in the manufacture of capsules to contain medication or for the coating of tablets, it may be colored with a certified color, may contain various additives, and may have any suitable gel strength.

Gelatin contains amino acids: alanine, arginine, aspartic acid, cystine, cysteine, glutamic acid, glycine, histidine, hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tyrosine, and valine. Because only traces of other important amino acids are present and tryptophan is absent, gelatin is an incomplete nutritional protein. The gelatinizing constituent is known as chondrin, and the adhesive substance is known as glutin.

Gelatin is a pharmaceutic aid (encapsulating agent, suspending agent, tablet binder, and coating agent). Combined with glycerin, it forms glycerinated gelatin; as such, it is employed as a vehicle and also for the manufacture of suppositories. Zinc oxide is added to form zinc gelatin, which is used as a topical protectant. In addition, gelatin is a nutrient and is extensively used for the preparation of commercial food products and for bacteriologic culture media.

Absorbable Gelatin Sponge

Absorbable gelatin sponge is a sterile, absorbable, water-insoluble, gelatin-base sponge. It consists of a light, nearly white, porous, pliable, nonantigenic matrix prepared from purified, specially treated gelatin, and is sterilized by heat. Even when handled roughly, this product shows little tendency to disintegrate. It absorbs about 50 times its weight of water and about 45 times its weight in blood.

Control of capillary oozing and of bleeding from veins is effected through the use of absorbable gelatin sponge applied in the dry form or saturated with sterile, isotonic sodium chloride solution or sterile thrombin solution. The sponge is applied to the bleeding area and held for 10 to 15 seconds, after which it is left in place.

Absorbable gelatin sponge is a local hemostatic. It is applied topically in operative wounds.

COMMERCIAL PRODUCT. Gelfoam®. This is supplied as individual sponges, dental packs, prostatectomy cones, and powder intended for a variety of uses (Fig. 10–2).

Absorbable Gelatin Film

Absorbable gelatin film is a specially prepared gelatin product used in neurosurgery and in thoracic and ocular surgery. It consists of a thin, pliable, nonantigenic absorbable film of purified gelatin. In the dry state, it resembles cellophane in ap-

Fig. 10–2. Complete operation of the manufacture of Gelfoam: preparing the gelatin (foreground), filling molds, baking, cutting the finished product into desired shapes, packaging, and sterilizing. (Photo courtesy of The Upjohn Company.)

pearance and stiffness and occurs in pieces about 25 × 50 mm or 100 × 125 mm in size and about 0.075 mm in thickness. When moistened by immersion in salt solution, it is easily cut into the shape needed to fit into the contours of the incision.

COMMERCIAL PRODUCT. Gelfilm®.

Microfibrillar Collagen

Microfibrillar collagen is a fibrous, water-insoluble material prepared from purified bovine corium collagen. It is an absorbable, topical hemostatic agent that is used in surgical procedures when control of bleeding by ligature or other conventional means is ineffective or impractical. It is applied dry and directly onto the bleeding surface; the microfibrillar collagen attracts platelets that adhere to the fibrils and trigger the formation of thrombi.

PROPRIETARY PRODUCT. Avitene®.

Absorbable Surgical Suture

Absorbable surgical suture is a sterile strand prepared from collagen derived from healthy mammals or from a synthetic polymer. It can be absorbed by living mammalian tissue but may be treated to modify its resistance to absorption. It may be impregnated with a suitable antimicrobial agent and may be colored by a color ad-

ditive approved by the federal Food and Drug Administration.

The USP lists specifications for labeling, length, diameter, tensile strength, and other requirements. This product is also known as **catgut suture, surgical catgut,** and **surgical gut.**

Nonabsorbable Surgical Suture

Nonabsorbable surgical suture is a strand of material that is suitably resistant to the action of living mammalian tissue. It may be composed of either natural or synthetic fibers; in some cases, metal wire is employed. The label must contain detailed information about the product.

Penicillamine

Penicillamine is D-3-mercaptovaline or β,β-dimethylcystine. It is a degradation product of penicillin-type antibiotics. This substance is a metal-chelating agent employed in Wilson's disease (hepatolenticular degeneration) to promote urinary excretion of excess copper. It is also useful in treating lead poisoning, and for reasons unknown, it is sometimes useful in cases of severe active rheumatoid arthritis that are refractory to conventional therapy. The usual dose in Wilson's disease is 250 mg, 4 times a day; a single daily dose of up to 1.5 g is used in rheumatoid arthritis.

PRESCRIPTION PRODUCT. Cuprimine®.

Heparin Sodium

Heparin sodium is the sodium salt of forms of a sulfated glycosaminoglycan of mixed mucopolysaccharide nature varying in molecular weights. It is usually obtained from the intestinal mucosa or other suitable tissues of domestic animals used for food by humans. Heparin sodium is a mixture of active principles that prolong the clotting time of blood, mainly through formation of a complex with the plasma protein antithrombin and by inhibition of other coagulation proteases.

Used for their anticoagulant activity, salts of heparin are the drugs of choice when an immediate effect is desired. Strengths of heparin sodium are labeled in USP units per ml, but the USP unit is not equivalent to the international unit (IU). Administration is by deep subcutaneous injection, direct intravenous injection, or intravenous infusion. The usual intravenous dose is 10,000 USP units initially, then 5000 to 10,000 USP units every 4 to 6 hours. Heparin sodium is available commercially in concentrations ranging from 1000 to 40,000 USP units per ml.

PRESCRIPTION PRODUCTS. Hepathrom®, Heprinar®, Liquaemin® Sodium, and Lipo-Hepin®.

Heparin Calcium

Heparin calcium is very similar to the product just described, except for the substitution of calcium for sodium in the preparation of the salt. It is said to be superior to heparin sodium in reducing the incidence of bleeding, hematoma formation, and discomfort at the site of injection. These claims require substantiation.

PROPRIETARY PRODUCT. Calciparine®.

Protamine Sulfate

Protamine sulfate is a purified mixture of simple protein principles obtained from the sperm or testes of suitable species of fish, usually those belonging to the genera *Oncorhynchus* Suckley, *Salmo* Linné, or *Trutta* Jordan et Evermann (Fam. Salmonidae). It has the property of neutralizing heparin. Each mg of protamine sulfate neutralizes not less than 80 USP units of heparin activity derived from lung tissue and not less than 100 USP units of heparin activity derived from intestinal mucosa.

Protamine sulfate is a fine, white or off-white, amorphous or crystalline powder that is sparingly soluble in water. It is an antidote to heparin and is administered intravenously. The usual dose, intravenously, is 1 mg for each 90 or 115 USP units of heparin activity, derived from beef lung tissue or porcine intestinal mucosa, re-

spectively, in 1 to 3 minutes, up to a maximum of 50 mg in any 10-minute period, repeated as necessary.

Protamine sulfate for injection is a sterile mixture of protamine sulfate with one or more suitable dry diluents. **Protamine sulfate injection** is a sterile isotonic solution of protamine sulfate.

Protein Hydrolysate Injection

Protein hydrolysate injection is a sterile solution of amino acids and short-chain peptides that represents the approximate nutritive equivalent of the casein, lactalbumin, plasma, fibrin, or other suitable protein from which it is derived by acid, enzymatic, or other method of hydrolysis. This preparation must have not less than 50% of the total nitrogen present in the form of α-amino nitrogen; for this reason, it may be modified by partial removal and restoration of the amino acids or by addition of one or more amino acids.

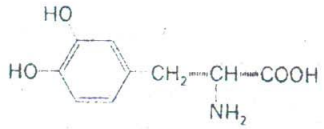
This drug is intended for use when the patient is unable to ingest or digest food to supply the nitrogen necessary to replace that amount lost through tissue metabolism.

Protein hydrolysate injection is a parenteral nutrient. The usual dose, intravenously, is 2 to 3 liters of a 5% solution daily.

PRESCRIPTION PRODUCTS. Amigen®, Aminogen®, Lacotein®, Travamin®, and Virex®.

Levodopa

Levodopa or 3-hydroxy-L-tyrosine is an amino acid that occurs in the seeds of *Vicia faba* Linné (Fam. Leguminosae), commonly referred to as the horse bean, the velvet bean, or the broad bean. Isolation of the compound from protein hydrolysate is somewhat difficult owing to its tendency to become oxidized; therefore, synthetic methods of production are employed. An efficient microbial conversion of L-tyrosine to levodopa has been reported.



Levodopa

High oral doses of levodopa have been effective in relieving parkinsonism; improvement in patients receiving up to 8 g daily ranges from modest to dramatic. Most symptoms are relieved to some degree, but akinesia and rigidity respond more readily than tremor. The major adverse effects noted include transitory nausea and vomiting, orthostatic faintness, and transient depression of granulocytes.

Symptoms of parkinsonism appear to be related to the depletion of striatal dopamine. Exogenously administered dopamine is either destroyed or does not cross the blood-brain barrier, but levodopa, the biosynthetic precursor of dopamine, does cross the blood-brain barrier. The action of levodopa presumably involves the decarboxylation in the neural ganglia of the amino acid to give the amine.

The usual dose, initially, is 250 mg, 2 to 4 times a day, gradually increasing the total daily dose in increments of 100 to 750 mg every 3 to 7 days as tolerated. The usual dose range is 500 mg to 8 g daily. Administration is in the form of capsules or tablets.

PRESCRIPTION PRODUCTS. Bio/Dopa®, Dopar®, Larodopa®, Levopa®, Parda®, Rio-Dopa®.

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