show a greater or less degree of calcification. Lime salts are also deposited in the dead fat cells in cases of fat necrosis. Calcification of the renal epithelium follows the cloudy swelling produced by such poisons as mercuric chloride, carbolic acid, bismuth, aloin, etc. Retained decidua or chorion, or portions of the dead fœtus and its membranes, may become calcified (lithocelyphopædion), or the sac may rupture and the fœtus escape into the peritoneal cavity, later becoming calcified (lithopædion). In diseases of the bones characterized by a resorption of the lime salts, the latter may be deposited in other tissues of the body.

Calcified tissues are hard and white and sharply outlined; the area affected may be large or small. The lime salts may be dissolved out by the action of acids, in the case of carbonates with the formation of carbonic acid. Microscopically, deposits of carbonates or phosphates stain deep blue or violet with hæmatoxylin.

A deposit of uric-acid salts occurs particularly in gout. The gouty deposits consist chiefly of sodium urate with small amounts of carbonate and phosphate of lime. The tendon sheaths, synovial membranes, ligaments, articular cartilages, kidneys, skin, and subcutaneous tissues are chiefly affected, but the deposits may ultimately be found in nearly every organ of the body. The larger deposits, called *tophi*, form large rounded masses, of a white, plaster-like substance, which are found particularly in the joints and tendons.

The individuals exhibited in museums as "petrifying" or "ossifying," are either cases of myositis ossificans or of scleroderma.

Petrifaction of the tissues of the body after death may occur under certain conditions, but is probably very rare. The majority of cases reported as such are in reality examples of adipocere formation. Very little is known with certainty regarding the petrifaction of the cadaver. Petrified or fossilized bones of the human race are very rare. Such have been reported to have been found in caves and in bog deposits whose waters were impregnated with iron and lime. In old bones there may sometimes occur a crystalline arrangement of phosphate of lime, or the bony structure may become so impregnated with mineral elements that its color and consistency become greatly changed. It is very probable, however, that a complete replacement of the elements of the bone or of the body tissues with mineral constituents is of very rare occurrence. (See also *Calcification.*)

Aldred Scott Warthin.

PETROLATUM.—The word *petrolatum* stands, both in Latin and in English, as the official title in the United States Pharmacopœia for an unctuous derivate of petroleum, obtained by distilling off the lighter and more volatile constituents of the oil and purifying the residue. Three grades of petrolatum are official, the difference being in consistence only. They are entitled, severally, *Petrolatum Liquidum*, Liquid Petrolatum; *Petrolatum Molle*, Soft Petrolatum; and *Petrolatum Spissum*, Hard Petrolatum. The first of these grades is of the consistence of oil; the second is soft, like lard, and corresponds to the well-known proprietary substances *vaseline* and *cosmoline*; and the third is hard, like cerate. When the word "petrolatum," without modification, is used in prescription, "soft" petrolatum is dispensed. Petrolatum consists principally of a mixture of paraffins (hydrocarbons of the formula C_nH_{2n+2}), but probably also contains some olefins (hydrocarbons of the formula C_nH_{2n}), which, by their softer consistence, tend to increase the unctuousness of petrolatum. Petrolatum is a whitish or yellowish material, more or less fluorescent, tasteless, and with no odor, except when heated when a faint odor of petroleum is perceptible. It is entirely amorphous, and, in fluid condition, makes a transparent liquid. It is neutral in reaction. It is insoluble in water; scarcely soluble in alcohol, or in cold absolute alcohol; but soluble in boiling absolute alcohol, and readily soluble in ether, chloroform, disulphide of carbon, oil of turpentine, benzin, benzol, and in fixed or volatile oils. When heated on platinum foil, it is completely volatilized without emitting the acrid vapors of burning fat or resin.

Petrolatum owes its medicinal value to its combining with the physical attributes of the semi-solid fats the chemical peculiarity of the paraffins, of being practically unalterable and indifferent to chemical agents. Petrolatum neither hardens nor turns rancid by exposure, and can be treated with any chemical likely to be prescribed medicinally in an ointment without being itself attacked thereby. The substance is therefore available, either by itself as a simple unguent, perfectly bland and changeless, or as the fatty basis for medicated ointments.

Edward Curtis.

PETROSULFOL is a sulphur-containing bituminous product closely resembling ichthyol, but with a less disagreeable odor. It is miscible with water or oil, and is used as a general succedaneum for ichthyol.

W. A. Bastedo.

PHAGOCYTOSIS.—Phagocytosis is the term applied to the ingestion of solids by living cells. That leucocytes were capable of taking up inert particles when introduced into the animal body or even when mixed with the freshly drawn blood of such animals as the newt had long been known, when Haeckel pointed out the similarity between such processes and the engulfing of food particles by unicellular organisms. Roser went further in suggesting that resistance to infection by bacteria and other living irritants was due to the phagocytic properties of the cells of immune animals.

It is to Metchnikoff and his followers, however, that we are indebted for much of our knowledge concerning this particular physiological function of cells. In his researches on the comparative pathology of inflammation phagocytosis in many types of organisms was studied and the capacity of their cells for dealing with various solid particles determined.

It does not lie within the scope of this article, however, to give *in extenso* the opinions held by Metchnikoff and others relative to immunity excepting in so far as they bear upon the mechanism of phagocytosis, the factors which influence it, the fate of the matters enclosed by cells, and the value of the process as illustrated in the life histories of organisms.

The Mechanism of Phagocytosis.—Before the ingestion of solid particles by cells is possible the two must be brought together. In the case both of the amœboid unicellular organisms and of the wandering cells of the higher animals, this is brought about by the attraction of the cell to the particles. (See the section on Leucocytes, under *Blood.*) The attraction exerted by particles upon motile cells is probably operative only over a limited area, and although there is some difference of opinion concerning the matter, it would appear that a certain amount of the solid particles being dissolved in the fluids containing the cells may stimulate them to approach the particles or under other conditions to repel them.

Amœbæ or other single-celled organisms are brought into the sphere of influence of food particles and bacteria by diffusion currents, and micro-organisms may by their own motility come into such a position as to be more easily engulfed. Jennings and Moore have shown that when paramecia and other infusoria pass by their own movements from a less attractive into a more attractive solution, they tend to remain there because their movement in the initial direction is arrested and reversed just as they are about to leave the agreeable environment. By a series of reverses they are kept swimming backward and forward across this attractive sphere and thus accumulate, not by initial attraction toward, but by inability to go away from, the agreeable environment. It remains to be proved whether any such explanation can be adapted to the accumulation of leucocytes in the neighborhood of bacteria and their toxins.

In the higher organisms provided with lymph or blood channels or both, the transportation of wandering cells to the vicinity of foreign particles is passive, although

their arrest at the margin of the vessel walls and their later emigration is an active process in response to stimulus. Fixed cells like the endothelium of the lymph- and blood-vessels, serous cavities, and the spleen pulp may throw out pseudopodia and entangle and ingest bacteria which are brought to them by the circulation. They may even bud off the large mononuclear leucocytes which are so markedly amœboid and phagocytic, but proof that these after engulfing bacteria or other particles may again become fixed is wanting. It is a common thing for a wandering phagocytic cell to be later engulfed with its contents by fixed cells, especially endothelial cells.

Phagocytosis is to be observed in a multitude of ways, but perhaps as simple a demonstration as any is a modification of that used by Kanthack and Hardy. A drop of fluid from the posterior lymph sac or peritoneum of a frog is withdrawn by a capillary pipette, placed in the centre of a clean cover-slip and lightly inoculated with a fresh culture of *bacillus anthracis, bacillus filamentosus*, or some other large non-motile organism. The drop is inverted over a vaselined hollow ground slide, or, better still, a ring of filter paper may be placed upon a slide and the drop of inoculated lymph inverted over the hole (Miss Greenwood's method). The filter paper should be thick enough to prevent the drop from coming in contact with the slide, and should be moistened with water from time to time to prevent the desiccation of the lymph. This method provides plenty of oxygen. Such a preparation may be kept under observation for hours at room temperature, and the leucocytes, of which in the frog there are fewer varieties than in mammals, remain active and may be seen to attack the bacteria according to a definite plan. A better method, especially for demonstration to large classes, is to inoculate a culture directly into the peritoneum of the frog and to withdraw drops for microscopic study from time to time. Observation may be made while the cells are living as outlined above, or smears stained with eosin and methylene blue may be prepared at various stages.

It will be seen that the coarsely granular oxyphile (eosinophile) and hyaline (large mononuclear) leucocytes are actively attracted to the chains of bacilli, the former being generally the first to attach themselves. Their granules exhibit streaming movements before, and usually disappear immediately after contact. The lymphocytes (small mononuclears) seem to take no active part, although they become included in the plasmodium formed by the other two varieties of leucocytes and the chains of bacilli which become bent into sharp angles and finally tightly compressed. The individual cells seen to become a part of the plasmodium, soon lose their outline, and in unstained specimens cannot be differentiated. The plasmodium later breaks up, and the component cells again become free in from five to nine hours. The coarsely granular oxyphile cells which have lost their granules and whose protoplasm has become amphophilic upon contact with the bacilli sometimes regain their granules with their oxyphilic reaction. In the hyaline (large mononuclear) cells, however, at this stage frequently one or more vacuoles can be seen which contain chains of bacilli doubled upon themselves so that from two to five or more bacilli are included. The included bacilli are undergoing degeneration as evidenced by their swollen, granular, or generally "wilted" appearance. Kanthack and Hardy after a very extended series of observations concluded that with fully virulent bacilli the coarsely granular oxyphile cell is called into action first, and through contact with the bacilli, by a process of "extra-cellular" digestion or neutralization, works them harm, after which phagocytosis on the part of the hyaline cells becomes possible. They maintained that this is true not only for frogs but for mammals, and were convinced that phagocytosis as the initial movement is possible only where non-virulent bacteria or other relatively inert particles are employed.

The difference in the *modus operandi* of these two leucocytes has been very graphically illustrated in a more recent publication by Hardy in which he was able to measure accurately under the microscope the rate of growth of chains of bacillus filamentosus (non-virulent) which had been introduced into a drop of frog lymph and observed under the microscope for a number of hours. He found that in those bacilli which had come into contact with coarsely granular oxyphile cells no growth took place. Those in contact with hyaline cells or lymphocytes grew out into long filaments, as did also the free bacilli. Where one end of a chain was enclosed within a vacuole of a hyaline cell growth in that direction was arrested, although division of the bacilli at the other end of the chain went on. It will be seen that the material ("slime") extruded or exuded by the coarsely granular oxyphile cell at the time of the disappearance of its protoplasmic granules, or perhaps, more correctly speaking, that contact of the bacilli with the changed protoplasm —true phagocytosis not taking place—had the same inhibitory effect upon the growth of bacilli as had the contents of the digestive vacuole of the hyaline cell. The vacuoles of phagocytic cells probably all contain a ferment. Such has been shown to exist in the food vacuoles of the amœba by Krukenberg, Reinke, and Greenwood. Further, the ferment fluid has been shown to be acid, although secreted by an alkaline protoplasm. In these vacuoles whatever is capable of digestion goes into solution and serves as food for the cell, while the insoluble remnants are extruded.

It is impossible to hazard any opinion concerning the exact nature of such digestive fluids or mechanism, particularly when considering the destruction by phagocytosis of bacteria against which animals have been rendered immune. It has been suggested by Ritchie as quite possible "that by virtue of one set of powers a phagocyte may kill a bacterium, by virtue of another set of powers it may digest it, and the latter process may be the same as ordinary proteolysis, as it occurs in connection with the intestinal glands of an animal." It must be remembered, however, that typhoid bacilli will develop in solutions of pancreatic ferment possessing sufficient activity to digest fibrin, and it is well known that in artificial digestions with all the common ferments antiseptics must be employed in order to prevent overgrowth of putrefactive and other bacteria. Certain observers, including some of the Pasteur school, even go so far as to suggest that nearly all kinds of ferment activity in the animal body are facilitated by, if not largely dependent on, the presence of bacteria.

One is therefore forced to ask whether the phagocytic inclusion and digestion of bacillus typhosus by the cells of an animal immunized against that micro-organism is accomplished in exactly the same manner and by the same ferment activity as would be the cholera vibrio had the animal been rendered resistant against that organism. It does not seem possible that by repeated immunizing doses of a given micro-organism the phagocytic cells can be so altered as completely to change their digestive mechanism. It is well known, however, that bacteria are frequently englobed, and later during their growth, or by their production of substances which may neutralize or destroy the digestive ferment, the phagocytes may be destroyed, although similar cells may later by a process of immunization acquire the property of seizing and also digesting the same bacteria.

Further discussion of these matters will be necessary in considering the questions of what cells are phagocytic, the fate of enclosed bacteria and other masses, the economic uses of phagocytosis, and the relation of phagocytosis to present-day theories of immunity.

What Cells are Phagocytic?

In unicellular organisms phagocytosis affords a means of securing food and for defence. In more highly developed organisms with the greater specialization in other functions that of phagocytosis is assigned to definite cells, particularly those of mesodermal origin. When micro-organisms or particles obtain access to the body fluids they may be carried to any part of the body unless dis-

posed of or arrested. Similarly, when irritant particles or micro-organisms are localized in the body, phagocytic cells and those with other defensive activities may be hurried to the front by way of the lymph and blood channels. It may be well to consider first the free or wandering cells which are phagocytic, and secondly those which are fixed.

1. Phagocytosis in Free Cells (see also section on Leucocytes under *Blood*). If we look upon phagocytosis as an active process the red blood cells may be excluded.

Lymphocytes (small) are not phagocytic. Their protoplasm is so scanty as to leave no room for inclusion of particles nor have they been shown to be actively motile.

Coarsely granular oxyphile cells (eosinophile), although infrequent in normal blood, are more plentiful in lymph, and in tissue spaces they are abundant. Kanthack and Hardy consider them to be never phagocytic. Mesnil, a pupil of Metchnikoff, states that they may be phagocytic. I have always looked upon them as never phagocytic until two years ago we encountered one undoubted case of inclusion in, and partial digestion of, *B. filamentosus* by one of these cells in an exudate resulting several hours after an intrapleural injection of the organism into a guinea-pig. The eosinophile granules were perfect, and the bacilli were contained within a vacuole. Phagocytosis on the part of these cells must be extremely rare. They appear to act rather by a process of extracellular paralysis or digestion of bacteria.

The finely granular oxyphile (*polymorphonuclear*) *leucocytes*, or "microphages" of Metchnikoff, are the chief phagocytes of the blood. Where irritants are applied to vascular areas these cells very quickly appear in the foci, emigrating rapidly from neighboring vessels. In pus formation, in the fibrinocellular exudates of diphtheria and pneumonia, and in exudates in serous cavities and many other sites, these cells are present in vast numbers. In pneumonia there may be present in the hepatized area many times the total number of these cells normally present in the whole body. Where do they come from? In certain infections the manufacture of these cells in the marrow of the long bones is tremendously stimulated (Muir, also Roger), so that following the initial temporary diminution of leucocytes in the blood the increased output is sufficient to supply all demands. The subcutaneous injection of staphylococcus pyogenes aureus into the tissues of rabbits, and serial observations on the resulting abscess formation (Hohnfeldt) afford an excellent opportunity of studying chemotaxis and phagocytosis in connection with these cells. Their phagocytic properties and modes of action may be studied in smears of gonorrhœal pus, in purulent fluid in cases of cerebro-spinal meningitis, and in pus from abscesses. The sequence of changes in inflammation in which finely granular oxyphile cells bear a part may be well observed when fluid from the abdomen is withdrawn from time to time after intraperitoneal injections of various micro-organisms (Pfeiffer, Durham, and others). These cells possess the capacity for engulfing carbon and other insoluble pigments and of digesting pieces of fibrin, cell débris, bacteria, and other soluble materials. Vacuoles, evidently digestive, may often be seen surrounding the particles, although not always. This variety of leucocyte is, in short, instrumental in the removal of inhaled pigment particles, hemorrhages into the tissues, fibrinous exudates, and other detritus, while in resisting the pyogenic micro-organisms it is probably the chief factor.

The hyaline (*large mononuclear*) *leucocytes* or "macrophages" of Metchnikoff are seemingly derived from the endothelium of vessels and from the spleen and lymphatic glands. The phagocytic work in those tissues where the transportation facilities of the blood stream are not readily available is dependent to a great degree upon these cells. Kanthack and Hardy believed that only in case of feebly virulent bacteria and non-irritant particles are they capable of immediate action. That they do operate after other cells have been engaged is evidenced by the fact that other cells, such as the finely granular oxyphiles, are very frequently found in various stages of disintegration enclosed within them. The intraperitoneal or intrapleural inoculation of non-virulent bacilli into guinea-pigs illustrates this well. Mallory believes that where an irritant of a low grade of virulence is present, proliferation of the fixed cells and phagocytosis are prominent features. In typhoid infection this is true, and hyaline cells are especially active phagocytes, the finely granular oxyphiles being inconspicuous. In tuberculosis and leprosy phagocytosis is common, and endothelial cells are particularly active. In purulent infections the finely granular oxyphile and not the hyaline cell is the chief phagocyte. In the lungs inhaled carbon pigment and broken-down blood pigment —in pneumonia of heart disease—are contained in large amounts in large flat cells with rounded or oval nuclei. Whether these are hyaline leucocytes or desquamated alveolar epithelium cannot always be determined. Hyaline cells are the connecting link between endothelium and leucocytes, and Muir has pointed out that in inflammatory leucocytosis increased activity in and production of hyaline cells can be found evidenced in the lymphatic sinuses of lymph glands and by the mitotic figures in free hyaline cells.

Other varieties of leucocytes have not been recognized as phagocytic, and, in fact, little is known concerning their activities.

2. Phagocytosis in Fixed Cells.—The endothelial cells are markedly phagocytic for bacteria and other particles which are brought to them in the blood or lymph. They engulf particles by throwing out pseudopodia, and within limits they are quite amœboid. It has been suggested that in extremely small vessels where the endothelium composes a large part of the vessel wall, vaso-constriction or dilatation may depend upon thickening or thinning of these cells as a response to direct stimulation by materials flowing in the blood or lymph. This, if true, has an important bearing not only on inflammation, but upon the vascular phenomena of fever. In considering the finding of pigment particles in fixed connective-tissue cells as in those of the supporting tissue of the lung, or in glands, there is a question as to their exact mode of entrance. It is among the possibilities that free leucocytes act as phagocytes and wander by way of blood or lymph channels or between or through other cells until the particles ultimately reach the location in which they are found. Or the original phagocytic leucocytes may have died and set free the pigment to be taken up by a second leucocyte, or by an endothelial cell, or by a connective-tissue cell. Or the original leucocyte with its contained particles may have been bodily engulfed by a growing connective-tissue or other fixed cell. Evidences of such a process are not wanting. In phagocytosis on the part of epithelium—superficial or in glands —the problems are just as complicated. When bacteria enter the liver through the portal circulation and are then engulfed and killed or attenuated by the liver cells and ultimately extruded or excreted into the bile capillaries, it is likely that the endothelial cells of the portal capillaries act first and that these yield up their contents to the liver cells. Whether epithelial cells such as those in the milk glands can take up living bacilli and excrete or secrete them in a virulent condition so that they are eliminated through the ducts, is a question. Adami has suggested that such is the case where tubercle bacilli are found in the milk of cows whose udders bear no evidence of tuberculosis. Many other matters bearing upon this question might be discussed, such as the methods of excretion of bacteria and solid particles by way of the kidney, tonsillar infection in tuberculosis, etc., but they do not lie within the scope of so limited an article as this.

The Fate of Enclosed Particles.—When insoluble pigment particles are found in situations to which they could not have been swept by currents of lymph or blood, amœboid phagocytes have probably been the carriers, and such cells may set free their contents either before or after death.

Undoubtedly through phagocytosis many bacteria are killed, but, as we have seen, not all of those which are

taken into the interior of phagocytes are destroyed. Metchnikoff has isolated single leucocytes which contained micro-organisms, and in a drop of broth under the microscope he has watched the bacteria increase within the cell until it was filled and finally destroyed, the micro-organisms escaping into the broth. In many cases of infection observation would warrant the belief that bacteria may be engulfed and carried considerable distances by phagocytes, which are then destroyed, the bacteria liberated, and a new focus of infection is set up. In many infections phagocytosis is pronounced throughout the whole course of the disease. This has constituted a difficulty for those who advocate the phagocytic theory of immunity. In such chronic diseases as leprosy, tuberculosis, and glanders, bacilli, apparently many of them living, are to be found enclosed in phagocytes. In epidemic cerebro-spinal meningitis and gonorrhœa—diseases of a more acute nature—one of the diagnostic points in connection with microscopic examination is the demonstration of the diplococci within the cells (finely granular oxyphile). It would therefore appear that while phagocytosis is undoubtedly an important factor in resistance to infection, there are distinct steps, namely, attraction of leucocytes which then engulf bacteria and later digest them. That digestion of bacteria does not always follow their enclosure in phagocytes is apparent.

The Factors which Influence Phagocytosis.—Anything which checks chemotaxis interferes with phagocytosis. It has been conclusively shown that highly virulent bacteria are less apt to attract wandering cells and induce phagocytosis than are more attenuated microbes of the same kind. For instance, if attenuated anthrax bacilli be inoculated in one ear of a rabbit and virulent anthrax bacilli be inoculated in the same manner and dose in the other ear of the same rabbit the results are quite different (Metchnikoff). In the one ear the attenuated bacilli induce a tremendous accumulation of leucocytes, while in the other ear fluid is poured out into the tissues with little or no attraction of leucocytes.

The state of resistance of the animal is also important. Immunization to anthrax renders an animal capable of responding to a dose of virulent bacilli by an accumulation of leucocytes, while a similar dose in an untreated animal induces a huge outpouring of fluid.

The presence of soluble bacterial products in a definite locality tends to favor the attraction of leucocytes from the neighboring blood-vessels, while the circulation simultaneously of the same materials in large quantities in the blood stream tends to prevent it. This is illustrated (Roger, Ruffer) by inoculating the bacillus of symptomatic anthrax into the subcutaneous tissues of a rabbit when leucocytes rapidly accumulate at the site of inoculation and abscesses result. If another rabbit be similarly inoculated, while in addition an intravenous inoculation is made, there is tremendous outpouring of fluid, but no leucocytosis at the site of the subcutaneous injection, and death results in a few hours. Hence phagocytosis is apt to occur when the invading bacteria are not too virulent, when the resistance of the host is great, and when the irritants and soluble products are present in much greater abundance at a point or points outside the vessels than in the circulating blood.

The economic uses of phagocytosis have been dealt with more or less fully in the preceding portions of the article, and need be only mentioned here. As a factor in nutrition evidences of the importance of phagocytosis decrease as we ascend in the scale of development. For instance, in the amœba observation would tend to show the extreme importance of phagocytosis in this connection, while in the higher animals proof that it takes a great share in the securing and assimilation of food is wanting, although such may yet be forthcoming. As has been stated, pigment and solid débris, such as exudates, hemorrhages into the tissues, dead cells, and tissues of all kinds are largely removed by phagocytes. In the spleen phagocytic inclusion of dead blood cells and animal and vegetable parasites is always demonstrable. Many more examples could be quoted were it necessary. In their attraction to, inclusion of, carrying away, and destruction of invading organisms the phagocytic cells may be exhibiting characteristics largely acquired in exercising their more physiological functions.

Phagocytosis in Relation to Present-day Theories of Immunity.—Ehrlich's brilliant experiments and deductions (see article on *Immunity*) have necessitated a remodelling of many of our ideas, and Metchnikoff in accepting Ehrlich's views has attempted to harmonize phagocytosis with the activities of complements and immune bodies. Ehrlich believes that immunity against bacteria (or other cells) depends upon the original possession or artificial induction of a special substance, "immune body," which firmly unites with the bacteria and thus enables another substance, "the complement," which is present normally in the animal to kill the bacteria. The immune bodies are more resistant to heat than are the complements. In the serum obtained from an immunized animal both immune body and complement may be found, although Metchnikoff believes that both are liberated from leucocytes (microphages and macrophages) by "phagolysis," and that in the body the final action of the complement on the bacteria takes place only within the cell during phagocytosis, even should the immune body have been free in the fluids.

It has long been known that bactericidal substances are more abundant in the leucocytes than in the fluids of the body. More recent work of Denys and Leclef seems to show that from rabbits immunized against streptococcus the serum when mixed with leucocytes from such an animal was no more destructive for streptococci than when mixed with the leucocytes of a normal rabbit, while by itself it was practically not bactericidal at all. Two antibodies seemed essential for the destruction of the streptococci: one was to be found in the immune serum, and the other was afforded equally well by the leucocytes of the normal or treated rabbit.

Bulloch's work on hæmolysis tends to show that in the rabbit an increase of finely granular oxyphile cells in the blood accompanies the formation of complement and that activity of mononuclear leucocytes is related to the formation of immune body.

There seems to be as yet no information available concerning the *exact* source of complement and immune body. We are not justified in assuming because a substance is bactericidal in test-tube experiments that it is operative as such in the body. We have seen already that the coarsely granular oxyphile cell acts deleteriously upon virulent bacteria, and that it is not markedly phagocytic. There are doubtless other cells which are antibacterial and non-phagocytic. In assuming that the same cells produce both immune body and complement, Metchnikoff is not borne out by the observed facts, although he admits that the former is more likely to be liberated into the body fluids than the latter.

The digestion of bacteria by phagocytes Metchnikoff apparently considers to be due to a ferment which seems to be the same sort of thing as Ehrlich's complement.

It is not quite clear whether his "cytases" include complement which remains fixed in the phagocytes, the immune body which under some conditions escapes into the fluids, and in addition special "stimulines," which acting on the phagocytes cause them to approach bacteria and engulf them. Ritchie, in his admirable critical review of the subject, asks very pertinently how the so-called education of leucocytes is brought about. He suggests that in the case of immunization by repeated intraperitoneal injections of cholera vibrios it is perhaps possible that in the later injections the especially active phagocytes may have been the same individuals engaged in the former encounters with the vibrios.

Although the life history of a leucocyte is probably short, he suggests that such "sensitized" leucocytes might even be attracted from distant parts of the body. It is easily seen that while admitting such possibilities he leans to the view that the active leucocytes in each succeeding injection are new ones probably derived from the bone marrow or lymphatic sinuses.

To limit the formation of the active substances of Ehrlich to the phagocytic cells of the body as Metchnikoff has done, further complicates an already complicated but otherwise satisfactory theory of immunity. There seems to be ample evidence that there are many other active factors in the protective mechanism than those afforded by phagocytosis. Phagocytes are undoubtedly important, but not all the phenomena of immunity can be expressed in terms of phagocytosis. *F. F. Wesbrook.*

PHARMACOPŒIA.* — (Greek *φαρμακοποιία*, from *φάρμακον*, medicine, remedy, and *ποιεῖν*, to make, to prepare; Latin, *pharmacopœa* or *pharmacopœia*; German, *Pharmakopöe*; French, *pharmacopée*; Spanish, *farmacopea*, etc.). A *pharmacopœia*, in the modern sense, may be defined as a work published by some recognized authority, for the purpose of securing uniformity in the kind, quality, strength, and composition of simple and compound remedies used in the practice of medicine. It may either be of a local character, or it may apply to a whole country. During the early history of pharmacopœias, the term was also often applied to works written or published by individuals, without the official sanction of governmental or professional authority. The Greek word *φαρμακοποιία* occurs in later Greek medical writings under its proper meaning, "the preparation of medicines," or "the art, or business, of preparing medicines." As the title of a book treating of this subject, however, it is probably not older than the beginning of the sixteenth century.

Ancient and Mediæval Precursors of Pharmacopœias.— While the ancient nations did not possess any works which could be fully set side by side with our modern pharmacopœias, yet the gradually accumulating mass of facts relating to the preparation and practical use of medicines resulted in the composition of numerous works which treated at least incidentally of this subject. In giving an account of the literature relating to the latter, we shall confine ourselves to those works the influence of which has, in one way or another, extended to our times.

Egypt has furnished us the oldest existing documents containing formulas and directions for the preparation of medicines. The oldest known is the *Papyrus Ebers*, dating from the year 1552 B.C. (see *Med. Rec.*, 11, pp. 247–251), which mentions a large number of simple remedies, and also contains numerous formulas of compounds, often in the form of regular pharmacopœial recipes, accompanied by signs and terms expressing weights or measures, precisely as is customary at the present day.

The *Medical Papyrus of Berlin* (see Woenig, "Die Pflanzen im alten Aegypten," Leipsic, 1886), written about 1350 B.C., contains a great number of formulas, with exact statements as to ingredients, and weights and measures. These formulas are for both internal and external remedies, including enemata. The remedies are mostly simples, plant parts, gums, resins, etc., with a few metals, liquors, and well-known liquids, including urine, bile, blood, and fæces of various animals.

In addition to these written documents, there existed also formularies sculptured in stone, one having been found upon the walls of a regular pharmaceutical laboratory or *ási-t* (see Woenig, *loc. cit.*, 372) in the temple of Edfu.

India.—An examination of the oldest Indian literature, that of the Vedas, Brahmins, and Sutras, reveals little but superstition as to both diseases and remedies. The principal medical works of the Hindoos, viz., those of Charaka and Sucruta, cannot be traced back beyond the eighth century A.D. (see *New Remedies*, 1876, 229), the foundations evidently having been derived from the Greeks. Most of these medical works are characterized, and their meaning is obscured, by the poetic or metrical style employed in them. Four or five centuries then elapse before we meet with any other notable writings of this kind. Among the later medical treatises the most important are "Ashtângahridaya," by Vâgbhata, and the "Bhâvaprakâca," by Bhâva, both of them only a few centuries old. These contain likewise many formulas interwoven in the text. Regular treatises on pharmacy, or formularies, are not numerous (to the former belongs the "Prayogâmrita" of Vaidyachintâmani, and others); but treatises on materia medica or glossaries of simples are much more common. The most extensive of these is the "Nighanturâja," by Narahari, of Cashmere, being a dictionary of products of nature, etc., with synonyms. Another smaller but useful work is the "Madanavinoda" of Madanapâla.

Greece.—The writings of Hippocrates (about 460–377 B.C.) were the first, as well as the most important, in the early history of Greek medical literature. Although none of his genuine writings is devoted exclusively to the preparation of specific medicines, numerous such directions are contained in them, and the pharmaceutical art became developed during the succeeding centuries in proportion as the rational treatment of disease, upon the foundation laid by Hippocrates, spread through the cultivated nations of Europe and Western Asia.

Of those works which are known to have exerted a permanent influence upon the formularies of later times, that of Andromachus of Creta, Nero's court physician, next requires mention, being a sort of poetic formulary. He also wrote a poem on Theriac and its preparations, which for centuries was highly influential in medical practice. About 65 A.D., Servilius Damocrates composed similar pharmacological poems, his compound of theriac, thus treated, being subsequently known as "Confectio Damocratis." In about 78 A.D., Dioscorides wrote his famous *ὑλικά* ("Materialia"), a most valuable cyclopædia of simples, which became one of the chief sources of pharmacological writers down to the Middle Ages.

The next important Grecian medical writer was Claudius Gallinus (131 to about 210 A.D.). His numerous writings exerted an influence equal to that exerted by the works of Dioscorides. Two of them treat especially "on the composition of medicines according to the places" (of application) "and according to classes." His numerous complex mixtures gave origin to the term "Galenical."

Of later writers, the more important are: Aëtius, of Amida, in Mesopotamia (sixth century A.D.), who gives numerous formulas for plasters, salves, etc.; Alexander, of Tralles, in Lydia (525–605 A.D.), and Paulus, of Ægina (seventh century A.D.), both of whom likewise quote many formulas in their writings. Passing now over several centuries, we find no author worthy of mention until we come to Nicolaus Myrepsus, of Alexandria (second half of thirteenth century A.D.), who compiled an "Antidotarium" (*δυναμερόν*), or formulary, containing not less than two thousand six hundred and fifty-six formulas, in forty-eight chapters. This work was written in Greek, but only the Latin translation has been published (first edition, Basle, 1549). It is also entitled "Antidotarium Magnum" (not to be confounded with the "Antidotarium Parvum" of Nicolaus Præpositus). In spite of its encyclopædic character, this formulary did not acquire as much reputation as the less extensive works of Mesue or of Nicolaus Præpositus.

Rome.—Previous to C. Plinius Secundus (23–79 A.D.) only the writings of M. Porcius Cato (234–149 B.C.) interwoven in agricultural treatises, need be mentioned. In the great work on "Natural History" by the former, many subjects relating to materia medica are treated. The "Compositiones Medicæ of Scribonius Largus" (first century A.D.) is the first literary production, having the nature of a formulary, of Roman origin. It contains the first correct description of the method of obtaining opium. A treatise by Rufus of Ephesus on cathartics was for a long time influential. Many other more or less important works by Romans were written in Greek.

Arabic Countries.—The Arabs were the first to develop the art of the apothecary and to establish regulations regarding the quality and price of his medicines, and specifying which of them were to be kept in stock for instant use. Their advent infused new life into the torpid condition of the medical and other sciences.

At the end of the ninth century, Shâbûr ben Sahl wrote a sort of dispensatory under the title of "Ibdâl" (Haji Khalfa, ed. Flügel, i., 142), and about the middle of the twelfth century Abû 'l Hassan Hibet-allah ibn Talmîd composed a similar work, entitled "Krabadin" or "Grabaddin" (Arabic, *qarâbâdîn*, or *qrâbâdîn*), which was commonly followed by Arabic apothecaries. The most important of these works was that composed by the younger Mesue (Mâswîyah el-Mârdinî, died 1015 A.D.), of Maridin, on the Euphrates, and of which only the Latin translation is extant, under the title "Antidotarium, seu Grabaddin Medicaminum compositorum." This remained for a long time the chief canon of pharmacy. It contains a large number of formulas arranged in twelve chapters, each treating of a different form (for instance, Pilulæ, Cerata, etc.) under which medicines are applied or administered. Not less than four Italian translations of this work appeared previously to the year 1500, and the Latin text was often reprinted.

The writings of the most celebrated of all Arabic physicians, viz., Avicenna (Abû 'Ali Hussain ben Abdallah, Ibn Sinâ, 978–1036 A.D.), also contain many formulas which were incorporated in subsequent collections.

Other writers, whose works contributed in this direction, were Ibn Wâfid el-Lachmî (about 1050 A.D.), called Albenguefit in mediæval literature, whose work on simples has been published only in Latin translation. Serapion the younger (Ibn Serâbî, about 1070 A.D.) was the author of a similar work, but this was much more esteemed and made use of than the former.

The most important Arabic writer on materia medica is Ibn Baitâr (about 1197–1248 A.D.). His work on simples and foods, based on his own observations and on the works of Greek, Arabian, Persian, and Syrian writers, is a perfect storehouse of information, and has exerted considerable influence upon the development of therapeutics and pharmacy among his countrymen.

Persia has little of interest to present in this direction. If we except a treatise on materia medica, based upon Greek, Arabian, and Indian sources, written by Alherwi (ninth century A.D.), we meet nothing of interest until the close of the seventeenth century, when Father Ange de la Brosse, de St. Joseph, published at Paris (in 1681) the "Pharmacopœa Persica, ex idiomate Persico in Latinum conversa." That this is no translation of an original Persian work has been recognized many years ago by Dr. Hyde, who supposed it to be the work of Père Matthieu. Leclerc ("Histoire de la Médecine Arabe," Paris, 1876, ii., 481) reports that it is a translation of an Arabic work existing in manuscript in the National Library at Paris. It bears internal evidence of the intimate acquaintance of the author with European medicines, some of which were probably then unknown to Persians, while others which were known (such as opium) are omitted. In 1771 Mir Mohammad Hussain, of Khorasan, wrote a Persian pharmacopœia, and subsequently an encyclopædia of materia medica ("Makhzan el-adwiya," "Treasury of Medicines") of considerable merit.

Mediæval Europe.—Up to about the fifteenth century the apothecaries in European countries situated to the north of the Alps did not prepare many compounds themselves, owing to the difficulty of importing the numerous, often bulky, and perhaps scarce, crude materials. They were in the habit of obtaining the finished preparations from Italy, where the art of pharmacy was in a flourishing condition. Among the works written during the Middle Ages, which either served themselves as pharmacopœias or formularies or at least contributed to their compilation, may be mentioned the following: The "Antidotarium" (also called "Antidotarium parvum," to distinguish it from the "Antidotarium" of Nicolaus Myrepsus) of Nicolaus Præpositus, of Salerno (first half of the twelfth century), consisting of about one hundred and fifty alphabetically arranged formulas for compounds. This compilation, together with Mesue's "Grabaddin" (see under Arabic countries), constituted the most celebrated formulary of the Middle Ages (first edition, Venice, 1471). Other important works of this period are the following: "Compendium Aromatariorum" (1st edition, Bologna, 1488), by Saladinus Asculanus, a useful and much used work, in which much attention is devoted to the description of drugs and their mode of preservation; "Luminare Majus," by Manlius de Boscho (1st edition, Venice, 1496), a highly esteemed dispensatory. A counterpart of this is the "Luminare Minus" (Venice, 1517), of Quiricus de Augustis de Torthona. The "Antidotarium Florentinum" (1st edition, Florence, 1489; often reprinted) is the first pharmacopœia or formulary published in Europe under governmental authority.

History of Pharmacopœias. — The literature of pharmacopœias is very extensive, and an exhaustive account is beyond the limits of this work. Yet, since a reliable list or sketch of at least the more important pharmacopœias is often of great use to those who have to consult medical works published in previous years, a condensed account of them is here given, arranged by countries; among the latter being included, for the sake of completeness, most of those which possess no regular pharmacopœia of their own, but use some other work either from choice or by command.

Note.—In quoting editions of the less important pharmacopœias, only the date of the first one is usually given. A plus sign (+) behind the date indicates that several editions followed. In some cases the date of several or of all editions is given. The word "pharmacopœia" is usually abbreviated to save space.

Argentine Republic.—This country possesses no pharmacopœia, although commissions have long been maintained, at least nominally, for preparing one. The "Farmacopea del Pais," although a mere fiction, has been legally recognized, and the French, Spanish, and Italian authorities are variously followed.

Austria-Hungary.—In 1729, the Vienna Pharmaceutical Society published a dispensatory under the title of "Dispensatorium Pharmaceuticum Austriaco-Viennense," which was repeatedly revised and reprinted. In 1739 appeared the "Dispensatorium Medico-Pharmaceuticum Pragense," which also saw several editions. An official pharmacopœia prepared by order of Government by Stoerck, Jacquin, and Well, was published in 1774 under the title "Ph. Austriaco-Provincialis." This was several times revised, and also translated into German as well as into Dutch, the Netherlands at that time forming a part of the Austrian empire. After the loss of the Dutch provinces a fresh start was made, and the first pharmacopœia proper appeared in 1812, under the simple title, "Pharmacopœia Austriaca." The subsequent editions appeared in—1814 (ii.), 1820 (iii.), 1834 (iv.; this being full of misprints was republished in 1836); 1855 (v.); 1869 (vi.).

A supplement to the Austrian Pharmacopœia was published in 1879, and a new edition (Editio VII.) went into effect on the 1st of January, 1890. The Austrian Pharmacopœia is rather small, comprising only five hundred and seventy-eight titles. Its text is in Latin. From the year 1795 a special military pharmacopœia was maintained, its last revision dating from 1872.

Up to 1871 the Austrian Pharmacopœia was valid for the whole empire, but in that year a separate volume was supplied for Hungary, and this was republished in 1888 under the title "Magyar Gyogyszerkonvy; Masodik Kiadas." This work comprises five hundred and sixteen articles, and possesses both Hungarian and Latin texts on opposite pages.

The first Croatian pharmacopœia was published in 1888, under the title "Hrvatsko-Slavonska Farmakopœa," being practically a duplicate of the Hungarian in Slavonic and Latin texts.

Belgium.—Previous to 1823, there existed the Pharmacopœia Belgica of 1659, and various pharmacopœias representing the different cities, as those of Brussels (1639+),

*This article is practically a reprint of those contributed by Dr. Charles Rice to the preceding edition of this work and to the Supplement (Vol. IX.); the records, I might add, have been brought up to date, and a few changes have been made in the interest of economy of space.—*Henry H. Rusby.*