with amboceptors from dog serum. So far as we know, all varieties of animals may produce hæmolytic amboceptors. Noguchi has demonstrated their presence, both normally and after immunization, in both vertebrates and invertebrates.

It is to the immune body that the specific action of immune sera is due. This may be shown by placing both chicken and guinea-pig corpuscles in a drop of serum from a rabbit immunized against chicken corpuscles. The nucleated corpuscles of the chicken can be readily distinguished from the corpuscles of the guinea-pig, and it will be found that they undergo hæmolysis, while the guinea-pig corpuscles do not. It may also be mentioned that in this process the nuclei of the corpuscles are not dissolved, only the cytoplasm containing the hæmoglobin being noticeably affected.

On the other hand, it is possible for a serum to contain at the same time a large variety of hæmolytic amboceptors. These may be present normally, in which case the serum has the power to dissolve many varieties of corpuscles; or the same effect may be obtained by immunizing the animal with several varieties of blood at the same time. It has been shown that here we have not one amboceptor capable of uniting with all the varieties of corpuscle, but rather there is a special amboceptor for each variety. If one is removed by saturating with one sort of red corpuscle, the serum can still dissolve all the other sorts.

Another interesting feature of the immune body is that animals may be able to produce a body hæmolytic for other individuals of their own species; for example, a goat immunized against the corpuscles of another goat may have its serum become hæmolytic for the corpuscles of that particular goat. Such a lysin is called *isolysin*, as contrasted with the *heterolysins* formed when animals of different species are used. Of great importance is the fact that an *autolysin*, that is, a body causing hæmolysis of the corpuscles of the animal providing the serum, has not been obtained, although many experiments have been made to this end. It can be readily understood what serious results would promptly arise if such autolytic bodies were formed, and it has naturally been suggested that such a condition may exist in certain instances of auto-intoxication. In various diseases, moreover, Eisenberg found that *isoagglutinins* were present in very variable quantities, yet there were no instances in which the individual's serum was hæmolytic for his own blood. It must be admitted that at present the reason for the absence of autolysins is not satisfactorily explained.

The time required for the development of immune bodies varies greatly, as also does the time of persistence after immunizing injections are stopped. In some instances hæmolysins may be found as soon as a day after injection of corpuscles for the first time, and they are usually present in a week. In certain experiments of Ehrlich the time when maximum activity of the serum was reached varied from seven to fifteen days.

Bordet and other French observers have claimed that the union between amboceptor and corpuscle is not chemical but purely physical, but this contention seems to have been quite completely answered by Ehrlich and his followers. Ehrlich illustrates the resemblance of the reactions of intermediary bodies to known chemical substances by a comparison with diazo-benzaldehyde. By means of the diazo group the benzene radical may be united to one set of substances, such as phenols, aromatic amines, etc., while by the aldehyde group a different set of substances can be combined, including ammonia radicals and HCN. Thus by having the diazo-benzaldehyde as an intermediary body phenol and HCN can be united, the phenol in this case assuming the place of the red corpuscle, and the HCN the place of the complement. In any event it seems certain that the union of the immune body is with the stroma alone, and as physical means have been found inadequate to cause the liberation of the hæmoglobin it is apparent that some chemical change results.

Of the two combining portions of the amboceptor, the one that has an affinity for the complement is referred to as the *complementophile* group, while the one that unites with the cell is called the *cytophile;* or, in the case of hæmolysis, as the *hæmophile* or *hæmotrophic* group. It seems probable that there are also intermediary bodies that have several combining groups, and are therefore not amboceptors, but triceptors, quadriceptors, etc.

By those who consider phagocytosis of particular importance in all processes of immunity, the observations of Savtchenko, that the immune body causes the phagocytes to engulf corpuscles with great readiness, is esteemed of much significance. This increased phagocytosis is manifested by leucocytes either in the body or in the test tube, and may explain, at least in part, the increased phagocytosis observed in many diseases. Whether the phagocytosis is increased because of alterations in the red cells, rendering them more chemotactic than normal, or to direct stimulation of the phagocytes, is unknown. The former seems more probable.

Immune bodies are capable of transmission from mother to fœtus, although there is no transmission from the male parent. A rabbit immunized before or during pregnancy to certain corpuscles may give birth to young possessing similar immune bodies, and it is possible for immune bodies to be transmitted by the milk. Normally existing hæmolytic and agglutinating properties may be transmitted from mother to fœtus, but they do not necessarily agree in proportion in the blood of each; they are usually less in the fœtus.

Complement.—Because of its property of causing solution phenomena in cells, whether corpuscles or other kinds, complement is generally considered as of the nature of a ferment, and this is supported by its susceptibility to heat, which is much the same as that of the known proteolytic enzymes. Many chemical agents, such as ten-per-cent. HCl, also destroy complement. Furthermore Delezenne has shown that the union of trypsinogen and enterokinase in the intestine, that results in the production of the active proteolytic ferment trypsin, is of exactly similar nature to the union of complement and immune body. On the other hand, after hæmolysis of red corpuscles no bodies are found that agree with those produced by either tryptic or peptic digestion, and the stroma is not ordinarily dissolved, but is deposited at the bottom of the test tube as a sediment, still retaining some of its original form. In solution of red corpuscles by the known proteolytic enzymes the hæmoglobin is attacked and much altered, while it is unaffected in serum hæmolysis. Again, the hæmolysin differs from a ferment, in that definite quantities of complement dissolve definite quantities of corpuscles, and do not have unlimited action as do the ferments; therefore it would seem that the complement enters into combination in the reaction, which ferments do not do.

The origin of the complement is unsettled, although there is much reason to believe that the leucocytes are one source, and perhaps the chief one. The complement content of peritoneal fluid seems to be increased if many leucocytes undergo dissolution in it, and this fact was the basis of the idea of a bactericidal substance, *alexin* (Buchner), that the leucocytes secreted. Ehrlich seems to have demonstrated that this alexin is the same as the immune body and complement, and not a single substance that by itself destroys bacteria. Aseptic inflammatory reactions have been found to increase both the bacteriolytic and hæmolytic complement of the blood, although it cannot be demonstrated that the exuded leucocytes are rich in complement. It has also been found that the complement content of the blood in disease varies often in direct ratio to the amount of leucocytosis. Removal of the spleen does not prevent either the presence of complement or the formation of immune bodies in experimental animals (Levin). Complement is present in the serum of cold-blooded animals.

Undoubtedly there is more than one sort of complement, although at first Ehrlich thought that the complement was one and the same for all cytolytic processes. In some sera saturation of all the complement possible with one variety of amboceptor still leaves the serum

containing complement that can dissolve corpuscles when the proper amboceptors are supplied. Again, serums have been found to possess complements with varying resistance to heat, some being indeed quite thermostable. In one serum, for example, immunized against a mixture of swine, sheep, and ox blood, Wendelstadt found that the complement for swine blood was more resistant to heat than that for ox or sheep blood, while the latter resisted HCl more. Normal horse serum was shown by Ehrlich to contain two complements: one specific for rabbit corpuscles, the other for guinea-pig corpuscles, which could be separated by filtering through a Pukall filter, as the guinea-pig complement alone passed through. This variability in filtration of complement indicates that the size or consistence of the molecules is not dissimilar to that of the enzymes, which are also variously held back by filters. Some complements have been found to diffuse through animal membranes, while others do not. It therefore seems that complement is not, as was at one time believed, a single, non-specific substance, but complements may be as numerous and as various as the intermediary bodies. However, one thing seems proved, namely, that the complement is not developed through the process of immunization, but is a constant constituent of the normal serum, although greatly fluctuating in quantity. In immune serum, as a rule, the amount of complement is inadequate to saturate the immune bodies present. As before mentioned, this deficiency may be met by adding serum from animals not immunized—serum which contains complement. As a rule the normal serum should be from an animal of the same species as the immune animal, but it is a remarkable fact that a proper complement may be obtained for immune serum of one animal from an animal of an entirely different species. For example, serum of a dog immunized against the corpuscles of a guinea-pig, after being rendered inactive by having its complement destroyed by heat, may be again activated by addition of normal guinea-pig serum; that is, the guinea-pig complement will unite with the dog immune body as well as will the complement from the dog.

Another important fact concerning the varieties and nature of complement has been furnished by Kyes, who demonstrated that red corpuscles may contain within themselves intracellular complements, *endocomplement*. Of equal significance is the related observation that *lecithin* will act as a complement for cobra poison. That a definite substance of known chemical composition may act as the complement is an important step, although lecithin must be more allied to thermostable complements than to thermolabile complements, which are the ones seemingly of most importance.

There are two groups in complement: one of which is united to the immune body, therefore a haptophore group, and another that acts upon the cell to which it is anchored, and called the *zymotoxic* group. This latter is analogous to the toxophore group of a toxin. As a matter of fact a complement is a toxin for the cell it may attack. As might be expected, therefore, just as toxoids are formed by degeneration of the toxophore group of the toxin, so also *complementoids* are formed by the degeneration of the zymotoxic group of the complement.

As before mentioned, the affinity between complement and intermediary body is less than between intermediary body and cell receptor, therefore the latter union occurs first. If the amount of intermediary body is largely in excess of the amount of complement the hæmolysis is greatly interfered with, because the excessive intermediary bodies unite with the complement; and as the cell receptors have all been at once occupied by intermediary bodies, the complement cannot become attached to the cell, since intermediary bodies do not unite with each other. This blocking off is referred to as *deviation of the complement*.

Regeneration of complement after it has been exhausted takes place in a short time. In rabbits whose serum was deprived of complement by injecting goat corpuscles until the complement had all been absorbed by them, it was found that complete regeneration may take place in from two to four hours.

Although the complement is the normal, constantly present constituent of the blood that probably protects the body against bacteria and other injurious agents, yet it is also capable of being harmful to the cells of its own creator. Snake venoms, for example, seem to owe their poisonous properties to the presence of large numbers of amboceptors of various sorts, and therefore to produce their violently injurious effects they require the action of complement, which is furnished by the poisoned individual for his own destruction. It is probable that there are other conditions in which the complement is an agent of harm rather than of protection.

The amount of complement in the serum of an individual varies in health, and even more so in disease. In phosphorus poisoning the power of the serum of the rabbit to destroy guinea-pig corpuscles is lost, because the corresponding complement is absent. Longcope claims that complement for typhoid and colon bacilli is decreased in many chronic diseases, which may account for terminal septicæmia. Alcoholism is also said to reduce the complement of the blood of animals. Undoubtedly the fluctuation of complement content of the blood is an important factor in determining susceptibility to infection.

An indication of how purely chemical is the union between the various substances implicated in hæmolysis is the observation by Hektoen that ions of Ca, Sr, Ba, and SO_4 combine in such a way with complement that it is unable to unite with the immune body, and thus they prevent hæmolysis. These inorganic substances seem to saturate the affinity of the haptophore group of the complement in the same way that amboceptors do.

Antihæmolysin.—Just as an antitoxin can be produced by immunizing cells against the toxins that injure them, so by immunizing the blood corpuscles against hæmolytic serum an antihæmolytic serum can be obtained. If heated serum is used an anti-immune body is obtained, that acts by combining with the cytophile group of the intermediary body and thus preventing the intermediary body and the corpuscles from uniting. If there are several intermediary bodies in the injected serum, antibodies may be obtained that are specific for each. These antibodies seem to be the receptors of the red cells that unite with the intermediary body in producing hæmolysis.

By immunizing against normal serum, whether heated or not, *anti-complement* is obtained which also is specific. Ehrlich has shown that this anti-complement acts by combining with the haptophore group, thus preventing the complement from being anchored to the cell by the intermediary body. Such anti-complement does not unite at all with the intermediary body, which remains in a condition capable of taking up fresh complement if it is provided. Again, resembling the production of antitoxin with toxoids, anti-complement can be obtained by immunizing with complementoid.

Not only can *anti-heterolysins* be obtained, but also *anti-isolysins*, if serum hæmolytic for blood of an homologous animal be used in immunizing. Since during normal conditions of life red corpuscles are continally undergoing dissolution, it may be that in everybody there really develop autolysins, which are prevented from causing extensive destruction of the corpuscles by the production of *anti-autolysin*. Besredka seems to have demonstrated the presence of such antibodies in normal serum, and suggests that such self-immunization may be an important process in protection of the body. In this connection it may be mentioned that there seem to be antiferments normally present in the blood that are perhaps of importance in preventing self-digestion of the tissues during life by the ferments of the body itself.

Agglutination in Relation to Hæmolysis.—The well-known agglutinating reactions of bacteria can be duplicated with red corpuscles. As with bacterial agglutinins the agglutinin seems to be, in Ehrlich's terms, a unicceptor; that is, it has but one group with affinity for other substances, as is the case with the toxins. Agglutinins for corpuscles are found to varying extent in normal

serum, as well as in serums specifically immunized against the corpuscles. Heating at 55° C. does not destroy the agglutinin, and in this way the agglutination can be observed independently of the hæmolytic processes. Agglutination also occurs at temperatures approaching freezing, when hæmolysis is inhibited. Agglutinated red corpuscles collect in rouleaux and clumps that unite with considerable tenacity, so that ordinary shaking will not break them up. In hæmolytic immune serum this agglutination precedes the hæmolysis, but the two processes are quite unrelated. Normal serum may contain agglutinins and not be at all hæmolytic, and the converse is also true. The mechanism of agglutination is not understood, but it is suggested that some chemical change in the substance of the corpuscle renders the surface adhesive, or that some physical change in surface tension accounts for the coaptation and adhesion of the corpuscles. As agglutination occurs in corpuscles that have been fixed in formalin or sublimate, it is probably not the proteid of the corpuscle that is affected, but the other ingredients of the stroma, of which lecithins and cholesterin seem to be the chief. Flexner and Noguchi found that if ricin, an agglutinator, was allowed to act for two or more hours it is still possible then to produce hæmolysis by serpent venom, but the stroma remains at the bottom as a white, conglutinated mass. From this it appears that agglutination brings about a kind of coagulation of the stroma.

Agglutination of the corpuscles during life may be of some pathological importance, for such masses of agglutinated corpuscles could readily produce capillary thrombi and emboli, which, if widespread, might create much disturbance. Many bacteria produce substances that are agglutinative for human red corpuscles, among them being typhoid, pyocyaneus, and staphylococcus. Flexner has found in typhoid fever thrombi that seemed to be composed of agglutinated red corpuscles, almost free from fibrin and leucocytes. Probably many of the so-called "hyaline thrombi" found frequently in infectious diseases are really composed of agglutinated, partly hæmolyzed red corpuscles.

Agglutination is also produced by certain vegetable poisons, including ricin, abrin, and crotin, and these have been found to produce thrombi of agglutinated red corpuscles. Of these substances ricin alone, although strongly agglutinative, has no hæmolytic action, showing the independence of the two processes. Snake venom, like most hæmolytic substances, produces marked agglutination, and here also the agglutinin is distinct from the hæmolysin.

(3) Hæmolysis by Bacteria.

Both pathogenic and non-pathogenic bacteria produce hæmolytic substances that are excreted into the fluids in which they grow. During many infectious diseases marked hæmolysis occurs, especially in those with septicæmia. After death the hæmoglobin of the blood goes into solution, and the resulting staining of the walls of the blood-vessels, and later of the tissues everywhere, is generally familiar. In the post-mortem hæmolysis probably the putrefactive organisms are chiefly concerned, although it is marked a very short time after death in many cases of septicæmia, particularly when the infecting organism is the streptococcus, and here probably the pathogenic organism is the chief cause of the hæmolysis. The hæmolytic action of bacteria can be studied both *in vitro* and *in vivo*. Among the best known are *tetanolysin*, *pyocyanolysin*, *typholysin*, *staphylolysin*, and *streptocolysin*, as they have been termed. Of these the case of pyocyanolysin is questionable because it has been described as resisting heat over the boiling point, and Jordan seems to have proved that the hæmolysis is ascribable to the alkalinity that this organism produces in culture media. Other bacterial hæmloysins are, however, destroyed by heat at 70° C. for two hours; that is, they are altogether different from ordinary cellular hæmolysins. G. Ruediger shows the following differences between streptocolysin and the hæmolysins of serum: Streptocolysin is not destroyed at 65° C. for one-half hour, and therefore is different from complement. When destroyed by heating to a higher point it cannot be reactivated by the addition of complement, thus differing from intermediary body. It is also different from intermediary body in that it does not combine with corpuscles at 0° C.; on the other hand it does combine at 6° C., but does not exert any hæmolytic effect until the mixture is raised to a higher temperature. This last observation indicates that the streptocolysin is similar in nature to the toxins, which exhibit the same phenomena. Other observations indicate that its structure is the same as the toxins, namely, a toxophore group and a haptophore group. In other words, streptocolysin is simply a toxin for red cells, which acts like bacterial toxins for other cells by joining directly to the cell receptors without the intervention of any intermediary body. As a similar structure has been shown for staphylolysin and tetanolysin, it is probable that the bacterial hæmolysins are all merely toxins with a particular affinity for red cells.

Secondary anæmia of the infectious diseases is probably to be explained largely by this hæmolytic property of bacterial toxins. Hæmoglobinuria also may be produced in the same way. Intravenous injections of filtrates of the saphrophyte, B. megatherium, will produce hæmoglobinuria in guinea-pigs.

(4) Hæmolysis by Vegetable Poisons.

A number of plant poisons are strongly hæmolytic; among them are phallin and helvillic acids from certain mushrooms; abrin, crotin, agaricin, saponin, solanin, and cyclamin. These hæmolytic poisons are not affected by heating at 100° C., and are therefore quite different from the serum hæmolysins. These substances are at present chiefly of interest from the laboratory standpoint, as being a distinct class of hæmolytic substances. Their mode of action is not clearly understood, but they seem to contain toxophore and haptophore groups like the true toxins.

(5) Hæmolysis by Venoms.

The hæmolytic power of venom derived from different varieties of reptiles has through recent studies been brought into the domain of biologic hæmolysis, and the result has been not only an understanding of the mechanism by which the lethal effect of these poisons is produced, but also perhaps the strongest support of the principles of Ehrlich's theory yet offered from outside sources. At the same time a new, easily controlled medium for research in problems of immunity has been provided. The most fundamentally important fact is the discovery by Flexner and Noguchi that the hæmolytic and other toxic agents of venom are themselves true intermediary bodies. By itself venom is not hæmolytic, but it requires the presence of complement to enable it to produce hæmolysis, and as the venom contains no complement, this necessary part of the poison is furnished by the serum that contains the corpuscles. This is indeed a remarkable fact, that the active part of the serpent's poison is furnished by the victim itself, and particularly so in view of the position that serum-complement usually assumes as a protector against bacteria. The existence of a widespread power against various animals implies that these venom intermediary bodies are capable of uniting with the complement of sera of varied animals, are *heterocomplementophilic*, in the language of Ehrlich's theory, and experiment shows this to be true. The probable source of these intermediary bodies is apparently in the serum of the serpents, as if they were secreted directly from the blood into the poison glands, for serum of poisonous snakes is found to possess intermediary bodies almost identical with those of the venom. The only difference is that while venom intermediary body combines with complement of nearly all serums, the serum immune body combines almost only with the complement of the serpent's serum itself (*isocomplementophilic*). Venom from cobra, rattlesnake, moccasin, and

copperhead possesses in each intermediary bodies that seem to be identical in nature, although they may vary in quantity. This explains the rather remarkable fact that serum of animals immunized against cobra poison, generally called *antivenin*, will neutralize the hæmolytic and many of the other properties of the venom of rattlesnake, copperhead, and moccasin. Antivenin acts as an anti-intermediary body, and by occupying one of its haptophore groups prevents it completing the union of complement and cell. In order of decreasing hæmolytic power for mammalian corpuscles come venoms from cobra, water moccasin, copperhead, and rattlesnake. These venoms are also agglutinative for all corpuscles tried, and agglutination will occur at 0° C. Exposure for thirty minutes at 75°-80° C. destroys the agglutinative property. In general, the hæmolytic power of the venoms for different sorts of corpuscles varies in inverse proportion to its agglutinative power. The hæmolytic intermediary bodies are remarkably resistant to heat, suffering but slight loss of power at 100° C. Each venom contains many intermediary bodies, seemingly different for each sort of corpuscle hæmolyzed, at least to a great part; no one sort of corpuscle can so saturate all the intermediary bodies that none is left for other kinds. After the intermediary body is attached to a corpuscle it can unite with many different sorts of complements, but only the one natural to its serum accomplishes complete hæmolysis. Leucocytes also are dissolved, and they seem to have specific intermediary bodies different from those that unite with red corpuscles, but the agglutinin for each seems to be the same. As the venom contains large amounts of intermediary bodies, when an animal is poisoned by a snake the complement is quickly taken up, and this probably explains the deficient bactericidal power of blood serum in this condition that permits the extensive infections so characteristic of snake bites. Antivenin will prevent this interference with normal bacteriolysis by occupying one of the groups of the intermediary bodies of the venom so that it cannot use up the serum complement.

The highly hæmolytic cobra venom can combine with complements contained within the red corpuscles, *endocomplement*, and so produce hæmolysis in the absence of serum complement. Kyes has shown that *lecithin* may be the constituent of the red corpsucles that acts as the complement.

In passing it may be noted that the effects of venom on nerve and endothelial cells, which with the hæmolysis constitute the manifestations of its toxicity, are produced in the same way as the hæmolysis. Amboceptors are present that unite complement to these cells, enabling it to attack them. As certain venoms are richer in one sort of intermediary body than others, so the effects of the bite of one kind of snake differ from those of another kind, *e.g.*, rattlesnake poison is particularly endotheliolytic, and therefore hemorrhages are a prominent sequence of the rattlesnake's bite.

Red corpuscles of the frog are not hæmolyzed by venom, and those of necturus (mud puppy) but slightly, agreeing with the known resistance of cold-blooded animals to snake bites.

Eel serum is remarkably hæmolytic, so much so that a quantity of 0.1 c.c. per kilogram of body weight will kill a rabbit or guinea-pig in three minutes when injected intravenously. Heating at 54° C. for fifteen minutes destroys the hæmolytic action, and, unlike ordinary serum hæmolysins the addition of complement does not restore its activity. Animals can be immunized against this serum. Introduced into the stomach, eel serum is not toxic. It can be dried and redissolved without losing its activity, but acids and alkalies readily destroy it. Mosso, who first discovered the toxicity of eel serum, called the unknown active principle *ichthyotoxin*.

Hæmolysis in Disease.—During health there is always going on a certain amount of destruction of red corpuscles that have outlived their usefulness; so in disease we may have to deal with either an alteration in the normal processes of blood destruction, or the introduction of entirely new processes. Although the place and manner of normal red corpuscle destruction is not completely known, yet it seems probable that there is relatively little hæmolysis within the circulating blood. When a red corpuscle becomes damaged it seems to become more susceptible to phagocytosis, and it is picked out of the blood chiefly by the endothelial cells of the sinuses of the spleen, hæmolymph glands, and bone marrow. Within these cells it apparently undergoes hæmolysis. Eventually the resulting pigment is split up by the liver, the non-ferruginous portion forming the bile pigments, while the iron seems to be mostly withheld to be worked over into new hæmoglobin. Whenever during disease red corpuscles are more rapidly injured than they are under normal conditions, these processes of normal hæmolysis are exaggerated and we not only find the phagocytic cells of the spleen and glands packed with them, but endothelial cells elsewhere and leucocytes also take on the hæmolytic function. At the same time there is an excessive production of bile pigment from the destroyed red corpuscles, which has an undetermined relation to the so-called 'hæmato-hepatogenous" jaundice. If hæmolysis is very excessive the blood pigment accumulates in other organs than the liver and spleen. When at one time over one-sixtieth part of the hæmoglobin of the blood is in solution in the plasma, it may escape in the urine, producing hæmoglobinuria.

The hæmolysis of the acute febrile diseases is readily explained by the demonstrable hæmolytic property of the products of the organisms that cause them, such as streptocolysin, staphylolysin, etc. Perhaps at the same time altered metabolic products may also play a part, but it does not seem probable from experimental results that the thermic condition *per se* has much effect. In malaria, although the parasites enter and destroy the corpuscles in which they live, yet this alone does not account for all the blood destruction of the disease, for the amount of anæmia is quite without relation to the number of parasites to be found. There is good reason to believe that the plasmodia produce hæmolytic substances that are discharged into the serum. In the primary anæmias hæmolysis seems to be the essential process, although the agents involved are at present unknown. Absorption of hæmolytic products of intestinal putrefaction or infection has always come in for much suspicion, without ever becoming completely established. Here also the hæmolysis seems to take place in the endothelial cells rather than in the vessels. In such a disease as pernicious anæmia there is much reason to assume that defective or abnormal hæmatogenesis is an important factor. Probably the anæmia of nephritis is the result of hæmolytic action of the retained products of metabolism, in which connection the hæmolytic properties of ammonium compounds may be recalled. In some diseases associated with anæmia it has been found that the blood serum of the patient is distinctly isohæmolytic, although isoagglutination seems to be more frequent. Such sera, however, do not seem to be autohæmolytic, at least in the test tube. The bloody fluids that can be obtained from cancers have been found to be hæmolytic, while antihæmolysin has been found in ascitic and pleural effusions.

In many forms of poisoning hæmolysis is a prominent feature; in some it seems to be the chief effect of the poison, *e.g.*, potassium chlorate and arseniuretted hydrogen. In severe extensive burns there may occur hæmolysis, and hæmoglobinuria may also result. The remarkable "paroxysmal hæmoglobinuria" is at present without satisfactory explanation as to the cause of the hæmolysis. The hæmoglobinæmia of "blackwater fever" has been the cause of much discussion as to whether the malarial parasite or the quinine is the cause, with a divided opinion resulting, although undoubtedly cases do occur in malaria without administration of quinine. After removal of the spleen hæmolysis by the hæmolymph glands exceeds that of the primitive spleen, causing an excessive destruction of red corpuscles (Warthin). This suggests that the spleen may normally dispose of some hæmolytic agent which acts either by stimulating phago-

cytosis or by so altering the red cells that they are particularly susceptible to phagocytosis.

The lesions produced in the organs of animals injected with hæmolytic agents are usually pronounced and quite characteristic. There is often a subcutaneous œdema, frequently blood-stained, and similar fluid may be present in the serous cavities. The fat is yellowish, and the muscles are darker in color than is normal. The spleen is usually much swollen, soft, friable, and very dark in color. The liver is usually swollen and mottled with red areas in a yellow background. The renal cortex is dark in color, even chocolate-colored, and the pyramids are comparatively light; in the urine is frequently hæmoglobin. In the lungs are often hemorrhages or areas resembling small infarcts. The blood may be thin and even distinctly transparent. Microscopically the red corpuscles are found in all conditions of degeneration, and often fused together. In the liver, besides patches of congestion, fatty changes are present if the animal lives long enough. Large phagocytic cells packed with red corpuscles are abundant in the spleen, as well as diffuse accumulations of blood, often fused, and pigment both free and in the cells. Pigment also accumulates in the renal epithelium, which also often shows much disintegration; congestion is prominent and hemorrhages into both interstitial tissue and glomerules are frequent.

Bacteriolysis.—It is not our purpose in this article to discuss the specific micro-organisms in this relation, but merely to indicate the relations of hæmolysis and bacteriolysis. Whatever has been said in preceding paragraphs about the mechanism of hæmolysis can be transcribed to apply to bacteria and bacteria-immune serum. Pfeiffer's observation of the solution of bacteria by serum of immunized animals was the precursor of the modern studies of hæmolysis and the extension of Ehrlich's theory. Indeed the chief reason for the great interest in hæmolysis lies in the understanding that whatever may be learned about hæmolytic processes can be directly applied to the processes of immunity against bacteria. Therefore we understand that in the serum of an animal immunized against bacteria themselves, and not merely their toxins, there is present an intermediary body that is specific for the injected organism. This intermediary body attaches itself to the bacterium by one haptophore group, and with the other anchors the complement of the serum which then destroys the bacterium. Now as during immunization only intermediary bodies are produced in excess, while the complement is not increased, it often may be that defence may fail because of deficiency in the amount of complement. This possibly explains why it has so far been impossible to secure immune sera that will protect against bacteria as effectively as antitoxin protects against toxin, for with toxin no complement is required. The results of decreased complement content would be an increased susceptibility to infection, and this is seen in snake bites, when the venom uses up the blood complement and the patient often succumbs to bacterial infection after surviving the direct effects of the poison. In chronic diseases Longcope claims that in the later stages the amount of complement is much decreased, probably accounting for the occurrence of terminal septicæmias.

It is probable that hæmolytic complement is quite distinct from that causing bacteriolysis, and that complements for different bacteria can be separated from one another as well as from the agglutinins.

Welch has suggested that possibly the bacteria in their turn may develop antibodies to the tissues and fluids in which they are growing. If so, we have a reasonable explanation of the development of toxic substances with marked action on specific cells of the host, *e.g.*, endotheliolysins, leucolysins, hæmolysins; and also the peculiar manner in which bacteria often attack only certain tissues, *e.g.*, multiple septic arthritis.

Cytolysis.—Red corpuscles being merely a particular sort of body cell it might be expected that lysins for other cells could be obtained in a similar manner, and such is the case. Such lysins are called by the generic term *cytolysins*, or *cytotoxins*, and are specifically indicated by the name of the cell concerned, as endotheliotoxins or endotheliolysins, hepatotoxins, nephrotoxins, etc. The lysins or toxins in this case are similar in composition to the hæmolysins, that is, an amboceptor and a complement group, and these groups are in all respects similar to the components of the hæmolysins except that the cytophile group of the amboceptor is specific for certain tissue cells rather than for red corpuscles. Such specific cellular toxins may be obtained by immunizing the animals against the tissue which is injected emulsionized into its peritoneal cavity; but, as with the hæmolysins, they may occasionally appear in normal serums of various sorts of animals. It is by no means as easy to determine the results with tissue cells as with red corpuscles, where the liberation of the highly colored hæmoglobin is easily detected. To some degree lytic changes can be observed in tissue cells under the microscope, but this is not usually very satisfactory. Another method of observation consists in injecting the immune serum into the body of an animal, and studying both the symptoms and the anatomic changes brought about in this way. The latter method has found the most general application. A disturbing element in all such experiments lies in the difficulty of securing tissue cells of one kind alone for injecting. For example, when hepatic-tissue suspensions are injected there are introduced at the same time endothelial cells, connective-tissue cells, and usually red corpuscles and leucocytes. Therefore an immune serum obtained in this way would contain immune bodies for all these cells, and it becomes impossible to ascribe any changes that follow its injection into an animal solely to effects of the hepatotoxins. While there are possible ways of avoiding many of these difficulties they have not been generally applied, and much of the earlier work is very questionable on this account. At the same time that cytolysins are formed agglutinins also appear, and agglutination of specific cells occurs as it does with bacteria and corpuscles. One of the earliest pieces of work in this direction was with sperm agglutinins, obtained by immunizing with sperm. Such serum, however, was not spermolytic. In view of the elementary condition of cytolytic investigations, and the afore-mentioned sources of error in much of the work that has already been reported, I do not feel justified in this article in more than briefly discussing the specific results so far obtained. It should also be mentioned that recently some investigators who have used care in avoiding hæmolysins, etc., in preparing specific sera have not been able to obtain as marked results as had been earlier reported.

Leucocytolytic Serum.—This may be obtained either by immunizing with leucocytes obtained from exudates or from the blood, or by using emulsions of lymph glands. The latter method introduces so many cells besides the lymphocytes that it is not desirable. Specific leucocytolytic sera agglutinate leucocytes and produce observable morphologic changes, in the way of solution of the cytoplasm and cessation of amœboid movements. Of the leucocytes the large granular cells seem most affected and the lymphocytes least. When injected into the peritoneal cavity such serum causes an apparent initial leucopenia, and later a decided leucocytosis in the peritoneal fluid. Corresponding with this, if bacteria are injected at the same time as the serum, resistance is found decreased, but later it is much increased. Such serum also contains anticomplement, according to Wassermann, indicating that the injected leucocytes contain complement. Leucotoxin obtained by immunizing against lymphatic tissue is very thermolabile, being destroyed by 55° C. for thirty minutes, and the serum can be only partially reactivated by the use of fresh serum. Undoubtedly leucotoxic amboceptors are present in many normal sera, and their presence in the serum of certain cold-blooded animals and in venom has already been shown.

Endotheliolytic Serum.—Every attempt at immunizing an animal with any sort of fixed tissue must of necessity

involve the injection of endothelial cells as well as those specific to the tissue studied. Therefore it is possible that cytotoxic serum so obtained will contain endothelial toxins and so complicate any results of *intra vitam* experiments. There is every reason to believe that endotheliolytic substances are produced in this way. Ricketts found that serum of animals immunized against lymph glands was toxic to endothelial cells, which was indicated by hemorrhages at the point of injection, and marked desquamation of endothelium when the injection was made into a scrous cavity. In snake poisoning the extensive hemorrhages are also due to an endotheliolytic principle, called by Flexner *hæmorrhagin*. This is destroyed by heating at 75° C., and is particularly abundant; in fact, the chief toxic agent in rattlesnake venom.

Lymphatolytic Serum.—This serum has been studied recently by Ricketts and by Flexner, immunizing animals with lymph glands. As might be expected from the nature of the injected glands the resulting serum contained endotheliotoxin, leucotoxin, hæmolysin, hæmaglutinin, leuco-agglutinin, and precipitins. When injected into animals this serum had a marked effect upon the spleen and lymph glands, producing great enlargement of these structures, which were also congested. The bone marrow was also somewhat affected, and when marrow was used in immunizing, the *myelotoxic* serum produced marked proliferative changes in the lymph glands as well as in the marrow. The changes produced in the leucocytes were the same as those described for leucotoxic serum, indicating that the different forms of leucocytes can combine with immune bodies produced against lymphocytes.

Nephrolytic Serum.—It has been claimed that if a kidney is destroyed by ligating its vessels or ureter the remaining kidney develops serious degenerative changes, which are not present if one kidney is entirely removed. This has been attributed to the development of nephrotoxic substances produced in reaction to the absorption of the injured renal tissue that has been left in the body. Other methods of renal injury have been thought to produce similar effects, and serum of animals with kidney disease was said to injure the kidneys of normal animals. From this basis it has been thought to explain the progressive nature of the chronic nephritides as the result of nephrotoxins produced through the absorption of the injured cells, and which nephrotoxins injure still other cells. Such a process, however, involves the production of cell toxins in an animal toxic for its own cells, that is *autocytotoxins;* and as it has so far been practically impossible to produce autolysins of other sorts, it is not altogether probable that the kidney is an exception. Furthermore, the latest writer, Pearce, was unable to produce *isonephrotoxins*, and could not corroborate the results said to have been found in the remaining kidney after ligating the vessels of the other. He did obtain an active *heteronephrolysin*, but also found that immunization with liver produced just as actively nephrolytic serum as immunization with kidney.

Neurolytic Serum.—Even so highly specialized cells as those of the nervous tissue seem to produce a reaction with the formation of immune bodies. Perhaps because any symptoms produced by action on the nervous system are so readily detected, and because of the advanced condition of our knowledge concerning the minute structure of ganglion cells, the results obtained with neurolytic serum have been particularly striking. Perhaps the most positive results are those of Ricketts and Rothstein, who found that serum of rabbits immunized against the brains or cords of guinea-pigs, when injected into the vessels of guinea-pigs was highly toxic, causing death with various symptoms only explainable on the assumption of nervous lesions. Microscopically the ganglion cells showed marked changes in those animals that survived the injection long enough. All the results so far obtained have been with heterogeneous serum. Venoms, particularly that of cobra, possess strong neurolytic substances, that are the chief toxic agents in most of the venoms (the rattlesnake excepted). This neurolysin can be removed by saturation with nervous tissue from the hæmolysin, and conversely the hæmolysin can be removed by saturating with red corpuscles, thus corroborating Wassermann's experiments with tetanus toxin and supporting Ehrlich's theory.

Thyrolytic Serum.—There are but few reports on this serum, but of these the latest, that of Portis, indicates that after removal of all hæmolysis as a factor there do occur changes in the nature of excessive absorption of colloid, and proliferation after the order of that seen in regeneration. However, the clinical picture of thyroidectomy was not produced in any case, and the anatomic changes were not great.

Numerous reports may be found indicating attempts with varying success to obtain sera toxic for other tissues. Among them may be mentioned *epitheliolysin* (for ciliated epithelium), *spermatotoxin*, *hepatolysin*, *cardiolysin*, *splenolysin*, and *syncytiolysin*. Attempts at the production of immune serum with adrenal by Abbott resulted only in a serum with great hæmolytic power, but with no particular effect on the adrenal. The principle in all is the same, but the results as a whole are not now in a state to warrant extensive consideration. In general, it can be said that it has not been found possible in this way to throw out of function one particular organ, with or without involvement of other structures. It must be borne in mind that we can have grave functional disturbances without corresponding anatomic alterations. There is no reason known why a group of receptors of essential importance to the functional manifestations of the cell may not be quite independent of vegetative functions; and with impairment of these alone there need be no visible cell changes. *H. Gideon Wells.*

Bibliography.

Excellent reviews bearing upon these topics, to which the reader is referred for the bibliography of the earlier works, are found in: "A Review of Current Theories Regarding Immunity," by James Ritchie, Journal of Hygiene, 1902, ii.; Ehrlich's "Croonian Lecture," in the Proceedings of the Royal Society of London, 1900, lxvi.; and in the book by Vaughan and Novy, "Cellular Toxins," 1902.
References to all the later literature of importance will be found in the reviews of pathologic literature by Hektoen, in Progressive Medicine, each year since 1900.

HEMLOCK, POISONING BY.—The water hemlock (*Conium maculatum*) is a small herb, belonging to the natural order *Umbelliferæ*. It must not be confounded with the hemlock tree (hemlock spruce), a well-known product of the forest regions of the United States. Conium maculatum is indigenous in Europe, but has established itself to a limited extent in other countries. It is regarded as the poison which was used by the ancient Athenians in putting to death certain criminals, and has become famous in consequence of its use in the case of Socrates.

The poisonous properties exhibited by several parts of the plant, especially the fruit, are due to several alkaloids, of which coniine (sometimes called coniin) is the most important. This is a distinct alkaloid, forming a series of salts, and is one of the few of its class that are liquid at common temperature and do not contain oxygen. Its formula is $C_8H_{17}N$. It is a colorless liquid, specific gravity about 0.880, not very soluble in water. It boils at a temperature considerably above that of water, and has a distinct rotatory action on polarized light. Its odor is usually said to be mouse-like, a rather vague description, but it cannot be more directly described, except to say that it is strong and disagreeable.

Cases of hemlock poisoning have been mostly accidental, parts of the plant having been mistaken for edible herbs, such as parsley. The recorded cases give diverse symptoms, and it is highly probable that mistakes have been made as to the identity of the plants in several instances. The following summary represents the marked features: Headache, vertigo, dilated pupils, a prickling sensation in the extremities, with gradually developing paralysis. This latter usually begins in the legs. The paralytic condition extends to the muscles of the trunk and neck, speech and deglutition become im-

perfect, and finally asphyxiation may occur by failure of the respiratory muscles. The mind is not much impaired until the latest stages of the case. Convulsions may occur at an advanced stage. A case may last several hours, but is likely to be much more rapid in its progress, death sometimes occurring in a few minutes. The poisonous dose is small, but cannot be accurately fixed from the data at hand. Probably one drop of coniine would be fatal to an adult in most instances if treatment was not promptly instituted.

Treatment must be of the type used for the alkaloids in general. Tannin and animal charcoal have some antidotal value, but the thorough washing out of the stomach will be found to be of most advantage and should be instituted as soon as possible. Artificial respiration may be required in the advanced stages of the case. The marked paralytic condition suggests the use of strychnine in very small doses hypodermically, but such treatment must be used with caution.

The detection of the characteristic alkaloid is a difficult matter, but its peculiar odor will be of value. More important, from a practical medical point of view, is the recognition of parts of the plant. These should be carefully examined, and compared with authentic specimens, or mistakes will be made, for species of Umbelliferæ are often difficult to differentiate. The post-mortem appearances are not characteristic. *Henry Leffmann.*

HUNYADI JANOS SPRING, AUSTRIA.—A mineral spring at Ofen, Hungary, a part of Budapest. The water bearing this name, so universally used, especially in this country, is one of the "Hungarian bitter waters"; others, almost as well known and obtained from the same locality, are the Franz-Josef and the Apenta. These three are the strongest of the bitter mineral waters, and are used either as a laxative or as a cathartic, the effects depending upon the quantity of the water taken. The active ingredients are the sulphates of sodium and magnesium. The following table shows the proportions in which they occur in the various Hungarian waters; and, for purposes of comparison, several other waters of like constituency are included.

ONE LITRE OF WATER CONTAINS:

	Sodium sulphate. Grams.	Magnesium sulphate. Grams.
Hunyadi Janos	22.55	22.35
Franz-Josef	23.18	24.78
Apenta	15.40	24.40
Puellna	9.59	10.85
Friedrichshall	6.05	5.15
Kissingen Bitterquelle	5.80	5.00

The following is an analysis of the Hunyadi Janos water by Professor Bunsen. One pint contains: Sodium carbonate, gr. 13.20; ferrous (oxide) carbonate, gr. 0.08; calcium carbonate, gr. 6.04; strontium carbonate, gr. 0.19; sodium chloride, gr. 11.54; potassium sulphate, gr. 1.67; sodium sulphate, gr. 128.97; magnesium sulphate, gr. 137.98; silicious earth, gr. 0.09. Total, 299.76 grains. Free and partly combined carbonic acid, 8.06 cubic inches.

Other well-known waters of like character are those of the Rubinat Condal, Rubinat Serre, and Rubinat Llorach Springs in Spain.

The taste of these waters is disagreeably bitter, much like a solution of "Epsom salts," although it is said to be somewhat modified by the presence of free carbonic acid and the other salts; at best, however, they are not a pleasant drink.

These sulphated bitter waters are much employed either as an occasional aperient, or in habitual constipation and in dyspepsia accompanied by constipation. They are also a serviceable laxative in small doses in pregnancy, arteriosclerosis, cardiac disease, and other morbid conditions in which an unstimulating laxative is desired. In large doses they are indicated where a rapid, full evacuation of the bowels is the end in view. In brief, in all the innumerable conditions in which a "dose of salts" is indicated, these bitter waters, which are practically a solution of salts, can be used. The usual dose of the strong bitter waters is from a half to one wineglassful taken on an empty stomach. In emergency cases a larger dose can be taken—from three-quarters to one tumberful. *Edward O. Otis.*

IRON, POISONING BY.—Metallic iron and those compounds of iron which are insoluble in water are not poisons. The soluble salts, however, though not active poisons, have an irritant action, and are capable of destroying life when taken in large doses and in a concentrated state. The continued administration of medicinal doses even produces, after a time, decided gastric disturbance. It is probable that all the soluble preparations may act as irritant poisons when administered in large doses. The most important, however, from a medico-legal point of view, are ferrous sulphate (copperas, green vitriol), ferric chloride (perchloride), which is used medicinally in the form of tincture, and the tannate in the form of ink.

The salts of iron are rarely administered for criminal purposes. Most of the reported cases of poisoning have been the result of accident, or of the use of the sulphate or the tincture of the chloride of iron in attempts at abortion. The symptoms which follow the administration of large doses of the preparations named are essentially similar to those produced by the irritants in general. There are a styptic taste in the mouth, nausea, vomiting, pain in the stomach and intestines, and purging. The evacuations are black, owing to the conversion of the iron salt into a tannate by the tannic acid of the food, or into a sulphide by the sulphureted hydrogen resulting from decomposition in the intestines. Irritation of the genito-urinary passages is sometimes observed. The tincture of the chloride of iron is more corrosive in its action than the sulphate, by reason, apparently, of the free hydrochloric acid which it frequently contains. Its injection into the cavities of the body, for the purpose of arresting hemorrhage, has proved fatal.

The amount of any of the preparations of iron required to endanger life is not accurately known, but appears to be quite large. In most of the cases in which the sulphate has been taken, the amount was unknown. Recovery has taken place after a dose of 31 gm. (℥ i.) of the sulphate (Christison). A case is reported in which 48 gm. (fl ℥ iss.) of the tincture of the chloride of iron proved fatal in about five weeks (Christison). Recovery has taken place after doses of 32–96 gm. of this preparation. The favorable issue is probably due, in many cases, to the early occurrence of vomiting.

The results of experiments on animals are not uniform. Gmelin states that 7.7 gm. (℥ ij.) of the sulphate of iron administered to dogs by the mouth caused vomiting only; that 2.6 gm. (gr. xl.) administered to rabbits produced no injury; and that 1.3 gm. (gr. xx.) injected into the veins of a dog produced no symptom whatever. Dr. Smith, however, states that 7.7 gm. will prove fatal to dogs when administered by the mouth or applied to a wound.

The post-mortem appearances are those of a simple irritant, and are confined, so far as has been observed, to the stomach and upper part of the intestines. In acute cases the contents of the intestines will probably present a black appearance, owing to the presence of the tannate or the sulphide of iron.

Iron is eliminated to some extent in the urine. A small amount only is absorbed in any event, the greater part escaping in an insoluble form with the fæces.

Treatment consists in the use of the stomach-pump, or of emetics if necessary. Magnesia or dilute solutions of alkaline carbonates should be administered as antidotes, and these should be followed by demulcents. *William B. Hills.*

LIPOMA (Adipoma, Steatoma) is a tumor consisting essentially of adipose tissue. Such growths belong to the mature connective-tissue tumors, and have for their

physiological prototype the adipose tissue found beneath the skin and serous membranes. Between normal adipose tissue and the fat tissue of lipomata there are no essential differences of structure. In the majority of lipomata the fat cells as well as the fat lobules are usually larger than those of normal adipose tissue (the former three to four times as large); but this difference does not hold good to such an extent that it can be used as a point in differential diagnosis. In general, a lipoma presents the structural characteristics of a localized mass of fat differing in no respect from normal subcutaneous fat. The chemical reactions of the fat contained in lipomata likewise correspond to those of normal fat.

Since the resemblance in structure to normal adipose tissue is so very close, it may sometimes be difficult to draw a line between a simple hypertrophy of adipose tissue and a lipoma. Both general and local hyperplasias of adipose tissue occur which are not classed with lipomata (general lipomatosis, lipomatous elephantiasis, the deposit of fat about an atrophic kidney or between the bundles of atrophic muscles); but other local hyperplasias of a similar nature have by various authors been styled lipomata. Thus the hyperplasia of the fatty capsule of the mammary gland which occurs sometimes in scirrhous carcinoma of this organ or in chronic interstitial mastitis has been called *lipoma capsulare*, an excessive deposit of fat beneath the epicardium has been styled *lipoma cordis capsulare*, and the deposit of fat in the villous fringes of the joints is known as *lipoma arborescens*, although analogous to the fatty hyperplasia so frequently seen in the epiploic appendages of the large intestine. Such local fatty hyperplasias may be styled *pseudolipomata*. An exact use of the term lipoma would limit its application to those formations of adipose tissue alone in which an actual new formation of fat tissue occurs. Such a criterion has, however, but little practical value, since in the fully developed growth of fat tissue it may be impossible to say whether the latter has arisen from a circumscribed hyperplasia or represents a true neoplasia. This difficulty is increased by the fact that lipomata are usually found in those parts of the body in which there is normally more or less fat tissue. A more practical guide will therefore be found in the principle that the term lipoma should be applied to *circumscribed proliferations of adipose tissue which show a certain anatomical and physiological independence of the neighboring tissue, even when the latter is fat tissue.*

The application of the term lipoma made by some writers to tumors other than connective tissue, the cells of which have undergone fatty degeneration or contain an abundance of fat, is wholly incorrect. The true lipomata belong to the mature connective-tissue tumors —that is, the tissue of which they are composed is of the type of adipose tissue.

HISTOGENESIS.—The histogenesis of lipomata is not yet definitely known. Their very frequent development in regions where fat tissue is normally found has led to the belief that the majority arise from a hyperplastic proliferation of adipose tissue with new formation of fat cells and fat lobules. Such an explanation would hold good even for the lipomata which are sometimes found in the submucosa of the gastro-intestinal tract, since in well-nourished individuals fat cells are usually present in small numbers in this region, and from these a lipoma could take its origin. Another view is that lipomata arise from undifferentiated embryonal cells which have persisted from fœtal life, or are formed by the proliferation of connective-tissue cells. The development of fat tissue from these follows the same course as that of the normal development of fat cells from fœtal myxomatous tissue. It is not improbable that undifferentiated "primitive fat organs" (developing fat lobules in the fœtal mesenchyma) may persist quiescent until adult life and later resume active proliferation, giving rise to localized growths of fat tissue which in their development would be more or less independent of the normal laws of nutrition and cell growth. Support is given to this theory by the fact that some lipomata in their growth appear to be entirely independent of the laws governing the general nutrition of the body, since they continue to increase in size or at least do not become smaller under conditions of cachexia, etc., when the normal fat tissue is being reduced in amount. The fact that a combination of myxomatous tissue and adipose tissue is frequently found under pathological conditions may also be taken as an indication of the close histogenetic relations of these tissues. In many lipomata areas of myxomatous tissue occur, and occasionally the appearances presented suggest the development of the fat tissue out of the myxomatous. Moreover, there are rare forms of lipomata in which the fat cells resemble those of embryonic adipose tissue, in that the fat droplets are of small size and do not coalesce into larger drops filling the entire cell.

A further origin for lipomata may be found in atrophic lymphadenoid tissue, a physiological paradigm being found in the development of fatty marrow from the lymphoid marrow, and the fatty transformation of the thymus, and later in old age that of the lymphatic glands. The relationship between lymphoid tissue and adipose tissue is very close. In the fœtus the development of the lymph glands is either coincident with that of the primitive fat organs or follows it; in the latter case the lymphadenoid structures (both ordinary lymphatic and hæmolymph nodes) developing out of the fat organs. In adult life under certain conditions a new formation of lymph glands takes place from adipose tissue, and in old age the lymph glands become to a large extent replaced by fat tissue. Throughout life it is very probable that there is a constant cycle of alternation between lymphoid tissue and adipose tissue. As the result of some disturbance of these processes it is possible that lipomata may arise, either from atrophic lymph glands or from anlage of undifferentiated cells. Askanazy traces the origin of multiple lipomata in particular to a replacement of lymph glands by fatty tissue.

The lipomata of the uterus, kidney-cortex, brain, spinal cord, etc., are to be referred to misplacements of anlage of fat tissue or of fibrous connective tissue which later undergoes a fatty metaplasia. Such lipomata are to be classed with the heterotopous teratomata. It should be borne in mind also that lipomatous masses not infrequently form the bulk of teratomata found in other regions as well.

ETIOLOGY.—As in the case of the other true neoplasms but little is known of the etiology of lipomata. Some of them may arise as the results of trauma or chronic inflammation. Such an origin has been ascribed to the fatty tumors sometimes found in the hands of working people in the parts most exposed to injury. In other cases fatty tumors have been found developing from scars. The fatty growths in the villi of the joints are usually associated with a chronic arthritis. There also seems to be some association between multiple lipomata and rheumatoid affections. In the case of the multiple and symmetrical lipomata a nervous or trophic origin is assumed by many writers. In such cases other symptoms suggesting a neuropathic origin are not infrequently present. According to Grosch, multiple lipomata of the skin arise from a disturbance of fat secretion by the skin glands due to a trophoneurosis. A connection between lipomata and disease of the thyroid and hypophysis has also been assumed by some authors. In the majority of cases it is very probable that lipomata are to be regarded as congenital, that is, they arise from misplaced anlage. A tendency to the development of lipomata appears also to be inherited in some families.

Gross Appearances.—All lipomata possess a more or less definite capsule. In the sharply circumscribed forms the capsule may be well defined, of varying thickness; in the diffuse forms the capsule is not perfect and often sends prolongations of connective tissue into the surrounding tissues, which if not removed may lead to a recurrence of the growth. The size of lipomata varies greatly; in the kidney, submucosa of the intestinal tract, etc., they may be very small, while in the subcutaneous tissues of the shoulder and back and in the retroperito-