(*c*) *Infections.*—The present article does not touch upon the subject of *Immunity* (which see). But there is in some persons a lack of susceptibility to various diseases which can be ascribed only to idiosyncrasy. This is well illustrated by vaccinia, there being a very few persons upon whom vaccination cannot be made to "take" no matter how often repeated. Some families of children escape in epidemics of the exanthemata, while others have these diseases several times, seeming to be unable to acquire the usual immunity from one attack. The universal exposure to the bacillus tuberculosis would indicate that the varying resistance of different individuals was largely a matter of idiosyncrasy.

(*d*) *Foods.*—There are many instances of idiosyncrasy as regards special articles of diet. One person, for instance, not only cannot eat cheese without violent gastro-intestinal irritation but cannot eat comfortably at a table where it is served. A special form in which these food idiosyncrasies assert themselves is in the production of urticaria from the use of them. Familiar examples are fish and shell-fish, especially lobsters; also strawberries and peaches. The latter fruit with some patients will cause an intense coryza apparently like a rose-cold. Herpes and angioneurotic œdema are similarly produced. Milk is an article of diet which many persons, generally mistakenly, think they cannot take. But there are really some who undoubtedly do have an idiosyncrasy against it. Regarding this as every other article of diet, a person should, often with medical supervision to guard against error, establish the fact of his own idiosyncrasy, and having once established it should thereafter respect it.

(*e*) *Drugs and Poisons.*—In this field idiosyncrasy may show itself either by an unusual susceptibility to a small dose, or, on the other hand, by a lack of susceptibility to the average physiological or even toxic dose. The former of these conditions is usually congenital; the latter may be either congenital or acquired. To it is given the technical name of "tolerance."

A high degree of tolerance is usually an acquired condition. It is well known that in both man and the lower animals, increasing doses of a toxin can be given till doses are tolerated far in excess of what would be fatal without such a progressive increase in dosage. The use of the toxin of diphtheria in the preparation of antitoxin is a familiar example of this. The same tolerance is established in the case of non-bacterial poisons, as, for example, tobacco, alcohol, and arsenic. But while such tolerance may appear to be present in certain organs or systems of the body, it may be absent in others. For example, the nervous system may appear to be resisting tobacco or alcohol, while the cardiac or digestive may be in reality succumbing to its use, or vice versa.

Such an acquired tolerance, whether in the case of toxins or of drugs, ceases soon after the regular administration of the poison has been stopped. The term Mithridatism was applied to a supposed immunity against poison gained by King Mithridates through the systematic use of poisons employed for that end.

The Styrian peasants have long been noted for their acquired tolerance for arsenic. One sceptical traveller is recorded to have administered seven grains of arsenious acid to an apparently healthy Styrian without ill effect. The enormous doses of morphine taken by morphinomaniacs of course suggest themselves in this connection.

A tolerance for one drug sometimes develops a tolerance for others of similar nature. To this may perhaps be ascribed the large amount of ether required to anæsthetize a habitual alcoholic. The writer once saw a morphine habitué who after taking nearly a drachm of morphine with suicidal purpose added to the dose over one hundred grains of chloral, to which he was not specially addicted, but the conjoined dose had no serious effect. Insensibility to large doses of sedatives, as ether, chloroform, opium, hashish, and bromides, is found in some persons not habitués of any of these drugs. Such persons are apt to be of a hysterical or emotional character. A lack of response to large doses of cathartics may be dependent on the cathartic habit or may be met with independently of it. People of warm climates are said to require exceptionally large cathartic doses.

Many persons are aware of their own drug idiosyncrasies, and may properly acquaint a strange physician with them. It is unwise to disregard such information if given by a person of intelligence. In doing so one is liable to repeat the disastrous experience of a previous attendant, and even if the experiment has no other ill-effect than the temporary discomfort of the patient, the latter is likely to feel provoked that his warning was not regarded. But of course the patient may have drug idiosyncrasies which are unknown to him. It is therefore unwise for a physician in case of untoward symptoms arising, to say offhand that they could not possibly be due to the use of a given drug, even though in his experience such a result had never occurred.

It may be said in passing that sometimes a pathological condition of some organ, involving too slow or too rapid absorption or impaired elimination, is at the bottom of what is regarded as a congenital drug idiosyncrasy. Thus renal inadequacy has been found in some persons who could not take iodine.

Childhood appears to present some special features with regard to drug susceptibility. Especially opium should be used very cautiously at this period. There is a common belief, on the other hand, that arsenic and belladonna are especially well borne by children. I think it very doubtful if this be true of the latter. Jacobi thinks children tolerate relatively large doses of quinine, digitalis, potassium iodide, and mercury.

It remains to mention a few specific drugs and poisons in regard to which marked individual idiosyncrasy is most often met.

Ivy Poison. Here all degrees of susceptibility are met, from perfect immunity to the most intense dermatitis following the slightest contact.

Alcohol. Here we find not only quantitative but qualitative idiosyncrasies One man can drink down all his fellows, while the others with an equal quantity of liquor may show either amativeness, quarrelsomeness, hilarity, or gloom.

Quinine is a drug which occasionally produces ill effects in a dose much smaller than ordinarily given. Such effects are tinnitus, deafness, blindness, and erythema. The writer has seen an intense universal dermatitis follow its use, and has known a clergyman in whom a dose of two grains invariably produced a marked erythema of the scrotum. Fever and abortion have both been reported to follow the use of quinine.

Salicylic acid will cause at times an intense delirium. I have seen it simulate an acute mania and last nearly a fortnight.

Belladonna also, as is well known, causes delirium in certain patients. *Opium* has caused vomiting, wakefulness, convulsions, and delirium. Doubtless there are some persons who should never take the drug. In the first use of the hypodermic syringe upon strangers a considerable conservatism is wise.

Potassium Iodide. Perhaps no drug reveals more of personal idiosyncrasy than this. Two to five grains often cause coryza. Four ten-grain doses have produced an œdema of the glottis severe enough to require tracheotomy. Fifteen grains a day will often cause a good deal of acne. But, curiously, patients who cannot take the small doses often can take the large one, and the massive doses of four to six drachms three times a day are generally well borne. One cannot insist too firmly that the tolerance for this drug is *not* a diagnostic criterion of syphilis. *Charles F. Withington.*

IGAZOL is said to be a mixture of formaldehyde, paraformaldehyde, and an iodine compound of unstated nature. It is in the form of a powder and was introduced by Cervello as a remedy for tuberculosis. Norway used it by vaporizing over a lamp for two hours three times a day. He reports good results in asthma, laryngeal spasm, and phthisis. It has no specific action.

W. A. Bastedo.

IGNATIA.—Saint Ignatius' Bean. The seed of *Strychnos Ignatii* Berg. (fam. *Loganiaceæ*). This is a large, half-climbing shrub, with very long, slender branches, and rather large, oval, pointed, three-nerved leaves. The flowers resemble those of *S. Nux vomica*, and the fruit is a very large (10 to 20 cm.), solid, many-seeded, hard berry. The plant grows in the Philippine Islands, and has been introduced into Cochin-China. The fruit appears to be not uncommon in some Asiatic markets. The seed has been known to Europeans since 1699 (Flückiger).

Saint Ignatius' Beans are hard, oblong, but irregularly faceted seeds, 2 or 3 cm. in length, of a dull yellowish-gray or blackish color, and corneous texture; they are normally covered with short, coarse, appressed, glistening hairs, but these are usually rubbed off before they reach this country, probably by the friction of the long voyage or carriage. The seed consists mostly of perisperm, but contains an oblong embryo, 6 or 8 mm. in length, in a cavity near the centre. The seeds have but little odor, and a very bitter taste.

Composition.—*Strychnine*, to the extent of from one to one and a half per cent.; *brucine* from one-half to three-fourths per cent.; considerable albuminoid matters; no starch. These seeds, from chemical, structural, and physiological points of view, are qualitatively so exactly duplicates of nux vomica that the reader is referred to that article for further information. Because it was supposed to be more uniform in its alkaloidal percentage, and in the relative percentages of strychnine and brucine, this drug was made official in 1880, but it was found impossible to induce physicians to substitute it for the familiar nux vomica, and it was dropped at the 1890 revision. An abstract, of fifty-per-cent. strength, dose 0.06 to 0.3 gm. (gr. i.–v.), and a tincture of the same strength and dose as that of nux vomica, were supplied.

W. P. Bolles.

IMMUNITY.—The past few years have added a great deal to our knowledge concerning the nature of immunity, but there is still much to be learned. Care must therefore be taken, while discussing the many plausible theories advanced, to remember always that they are but theories and may be, however interesting, still untrue.

Experience and observation have taught us that various races of animals and men, and various individuals among these, differ in their susceptibility to certain diseases; and, further, that the same individual is at one time more resistant to such diseases than at another. This inborn or spontaneous refractory condition is termed natural immunity, in contradistinction to that acquired during an attack of disease.

As in bacteria we distinguish between the ability to produce poison and the power to multiply, so in animals and man we may distinguish between immunity to poison and immunity to the invasion of bacteria.

With regard to variations in susceptibility, certain facts have been ascertained. Thus, cold-blooded animals are generally insusceptible to infection from those bacteria which produce disease in warm-blooded animals, and *vice versa*. This is explained in a measure by the inability of the bacteria which grow at the temperature of warm-blooded animals to thrive at the temperature existing in cold-blooded animals. But differences are observed not only between warm-blooded and cold-blooded animals, but also between the several races of warm-blooded animals. The anthrax bacillus is very infectious for the mouse and guinea-pig, while the rat is not susceptible to it unless its body resistance is reduced by disease and the amount of infection is great. The inability of a micro-organism to grow in the body of an animal does not necessarily indicate, however, an insusceptibility to its poison; thus, for instance, rabbits are said to be less susceptible than dogs to the effects of the poison elaborated by pneumococci, but these bacteria develop much better in the former than in the latter. Differences in susceptibility are sometimes very marked among different varieties of the same race of animals, as, for instance, between different kinds of rats and pigeons to anthrax. In animals, as a whole, experiments have shown that the young of all species are on the average less resistant to infection than the older and larger ones.

The difficulty experienced by many micro-organisms in developing in the tissues of the healthy body can be to a great extent removed by any cause which lowers the general or local vitality of the tissues. Among the causes which bring about such lessened resistance of the body are hunger and starvation, bad hygienic surroundings, exhaustion from overexertion, exposure to cold, the deleterious effects of poisons, bacterial or other, acute and chronic diseases, vicious habits, drunkenness, etc. Purely local injuries, such as wounds, contusions, etc., give a point of entrance for infection, and also through tissue injury one of less resistance, where the bacteria may develop and produce local inflammation. Local disease processes, such as endocarditis, may also afford a weak spot for the bacteria to seize upon. The presence of foreign bodies in the tissues in like manner predisposes them to bacterial invasion. Interference with free circulation of blood and retention in the body of substances which should be eliminated also tend to lessen the vitality. In these and other similar ways animals which are otherwise refractory may acquire a susceptibility to bacterial invasion.

Just as all conditions which are deleterious to the body lessen its power of resistance to bacterial invasion, so all conditions which are favorable to it increase its resistance, and thus aid in preventing and overcoming infection. The internal use of antiseptics against bacteria has not proved successful, for the reason that of all known non-specific bactericidal substances an amount sufficient to inhibit bacterial growth is found to be poisonous to the tissue cells. The efficacy of quinine in malaria and of mercury in syphilis is, possibly, an exception to the rule, but in both cases we are dealing probably with animal parasites, not bacteria. Such substances as nuclein and others contained in blood serum, when introduced into the body in considerable quantity, aid somewhat in inhibiting the growth of many bacteria. Even bouillon, salt solution, and small amounts of urine have a slight inhibitory action. The hastening of elimination of the bacterial poisons by free intestinal evacuation and encouragement of the functions of the skin and kidneys are also of some avail. The enzymes formed by certain bacteria have been found to exert a slight bactericidal action, not only on the germs which have directly or indirectly produced them in the body, but also on other varieties. None of these enzymes is sufficiently protective, however, to be of practical value nor equal in power to the protective substances formed in the body after infection with many micro-organisms.

The tissues of the animal body under the normal conditions of life are unsuitable for the growth of the great majority of bacteria, and are only fairly favorable to the development of the few remaining. Indeed, only a very small number of varieties of bacteria find the conditions really satisfactory, and even these must gain a point of entrance.

In seeking for a reason for the difficulty experienced by the bacteria in growing in the tissues, we cannot expect to find it in either the lack of or concentration of the nutritive substances, in the temperature, or in the reaction; for although these conditions may be unsuitable for some bacteria they are suitable for many, and thus cannot constitute the fundamental explanation of immunity. A possible reason for the inability of the bacteria to invade living tissues may be in the fact that the nutritious material in the living cells is in a form which the bacteria cannot readily assimilate; but if this be true it does not adequately explain why the bacteria do not develop in the nutritious fluids so abundant about and in the body tissues. We are thus driven to the conclusion that the body fluids themselves contain substances which are directly deleterious to the bacteria. As to the origin of these substances, it is conceivable that they may be either regularly produced in the cells or that they may be pro-

duced only when the body is invaded by micro-organisms. They may then remain unaltered in the fluids or be quickly eliminated. More than one of these things may actually occur.

The bactericidal effect of sera upon most bacteria is shown by the fact that when injected into the blood they begin to die at once, and this often continues until in a few hours all have died. Even when bacteria produce infection there is usually for a time a decrease in the number of bacteria living, but this is soon followed by a progressive increase. This fact can be observed not only in the blood and peritoneal cavity, but also when the bacteria are enclosed in animal or vegetable capsules, where the serum passing into them destroys the bacteria. The bacteria are killed even if they have previously grown in blood serum. Bacteria have also been injected into a vein carefully ligated above and below, and here without coagulation the blood exerts bactericidal properties. Even spores are killed in a few days. The effect of the fresh unheated blood serum can also be watched outside of the body. Here some species of bacteria die quickly, some slowly, and some lose only a portion of their number, and here the remaining portion after a time rapidly increases. The number of bacteria introduced is of great importance, for the serum seems capable of destroying only a certain number and after that loses its bactericidal properties.

If the bactericidal effect of the serum outside the body always went hand-in-hand with the immunity of the individual from which it was taken, the problem of immunity would be more easily solved, but this is not wholly the case. We must therefore add to the serum the activity of the cells which constantly produce the antiseptic substances which are given up largely to the blood and fluids of the body. This deleterious action of the blood on bacteria can be increased or diminished by infection, thus indicating living-cell influence.

Concerning the nature of these protective substances, named *alexins* by Buchner, we have as yet little positive knowledge, but certain properties of them are known. They are precipitated by a forty-per-cent. solution of sodium sulphate. A bactericidal serum affects in a deleterious manner the red blood cells of a different species of animals. These substances would seem to belong to the proteids and resemble certain of the globulins in their properties, but they are evidently extremely complex in their nature.

Their source is generally attributed to the cells, but probably certain cells only produce them. The red blood cells, for instance, seem rather to destroy than to increase them. The nuclein derived from the cells, although it has a general bactericidal action, does not belong to the specific alexins. The cells which have abundant nuclear substance, such as the leucocytes and lymph cells, seem especially to be a source of the alexins. Buchner and others have found that, through the irritation of bacterial filtrates, the leucocytes were attracted in great numbers to the region of injection, and that the fluid here, which was rich in leucocytes, was more bactericidal than the blood serum elsewhere. The same fluid acted also more perfectly when it contained numbers of leucocytes than when they were filtered out. Substances similar to the alexins are apparently derived from the leucocytes and their attraction to the injected areas gives to that location greater protective power. Still it has not yet been positively established that the specific alexins are derived from the leucocytes. The attraction between the leucocytes and the bacteria is rather due to the chemical attraction of the bacterial cell products and the bacterial body substance. Some chemical substances not derived from bacteria have also this quality, called positive chemotaxis, while others repel the leucocytes—negative chemotaxis. The theory of Metchnikoff that the leucocytes are the only actual protective bodies which ward off disease, and that they do this by attacking and devouring the bacteria, has been somewhat modified by more recent knowledge, and it is now believed that the bacterial substances attract the cells and that when these are brought together the general, and perhaps the specific, bactericidal property of the blood is thereby increased. The death of the bacteria liberates this positive chemotactic substance, and the death of the leucocytes gives rise to an increase of the non-specific bactericidal bodies. Thus we find that phagocytosis is most marked when the disease is on the decline or the infection mild, but that in rapidly increasing progressive infection it is usually absent. This would seem to indicate that the course of the infection is already determined before the leucocytes become massed at the point of its entrance. The first determining influence is given by the condition of the tissues and the bactericidal substances contained in them, and then later, in cases in which the infection is checked, comes the additional bactericidal substance given off by the attracted leucocytes. In so far as the tissues themselves are unsuitable for the development of bacteria they are sufficient to ward off infection, but in proportion as they are incapable of doing this they are assisted by the substances contained in the leucocytes. If the tissues are wholly adapted for the growth of the bacteria, neither they nor the leucocytes, nor both combined, can furnish sufficient protective substances to prevent the bacterial increase. The entrance of bacteria into the leucocytes, which is not infrequent, may mean the destruction of the former; but, on the other hand, the bacteria may increase in the white blood cells and destroy them, and they may be killed without entering the cells. The simple absorption by the cells is not necessarily a destructive process.

No explanation can as yet be given of natural immunity to bacterial poisons, except that it may be connected with some general property of the protoplasm of the cells which renders a combination between certain molecules of the cell and the poison impossible; thus, if tetanus toxin is injected into a susceptible animal it has been found that it will disappear from the blood in a few minutes. If the cells are subjected to suitable processes the tetanus poison will be found present in all the cells except those of the nervous system. In these it has apparently disappeared. As these are the cells that received injury from the toxin it is fair to assume that some chemical combination has occurred between them and the toxin. There is far less variation among different species in their resistance to the bacterial poisons than in their suitability for the growth of the living bacteria which produce them. Possibly certain organs, such as the lymph glands, the liver, etc.—may have some destructive power with regard to poisons.

By what means are virulent bacteria enabled to increase in the body, notwithstanding its protective powers, when non-virulent organisms of the same species are incapable of so doing? This is but little understood, but experiment shows in the first place that both virulent and non-virulent forms are equally resistant to general destructive agencies; and, secondly, that the bacteria are capable of producing substances (*lysins*) which neutralize in some way the protective substances (alexins). The virulence of bacteria would, therefore, depend partly upon their ability to produce these lysins, which act perhaps as the ferments upon the alexins, or perhaps combine with them. That bacteria under certain conditions form specific poisons, and under others, even when they grow luxuriantly, do not, is clearly shown by our experiments on the production of diphtheria toxin. Here it was found that when the bouillon was either a little too alkaline or too acid, though the bacilli grew rapidly, they did not produce specific toxins. When the bacilli were grown for a time in such bouillon they eventually became able to develop toxin in a soil in which they previously failed to do so. Similar cultivation in the body may be assumed to increase their ability to produce specific poison after a while under what would at first be adverse conditions.

With regard to the increase and decrease of general, and perhaps also of specific immunity, we have reason to believe that as the protective substances are produced through the action of the living cells, anything which

lowers the general vitality must lessen the vitality of the cells, and thus their ability to produce protective substances in the amount possible in a normal condition.

Specific Immunity.—The following theories have been advanced concerning the nature of specific immunity: The theory that a second infection is impossible because the first used up substances which were necessary to the growth of the bacteria is untenable for many reasons. Thus it can be demonstrated that the injection of a small amount of specific serum, which robs the tissues of nothing, produces the same immunity. Again, the injection into the body of a sufficient number of bacteria pathogenic for the animal selected gives rise to an infection in all cases.

The original theory of Metchnikoff, that the leucocytes or wandering cells of the body, after an infection with a certain variety of bacteria, become influenced in some way, so that they attack especially that form of infection again and destroy the bacteria (phagocytosis), can no longer be regarded as more than a very partial explanation, and can be accepted only by assuming as proven a number of hypotheses.

The retention theory of Wernich and Chaveau, somewhat modified, has most to support it. They have shown that the chemical changes in the blood serum of animals recovering from an infection are of such an extent as to be capable of being demonstrated experimentally, and these changes have been shown to persist for a number of weeks or months or even years. Similarly the serum of immunized animals retains for a long time its immunizing substances. We are therefore compelled to accept the fact that when an infection is passed through there are more or less protective chemical substances left in the blood which remain there for a considerable time. Kruse believes that these substances have the power of neutralizing the poisons which are given off by the bacteria upon their entrance into the body, and of thus robbing these poisons of their deleterious effects on the alexins; the body fluids in this way remaining antagonists to the growth of the bacteria, the alexins being bactericidal. If only a small amount of antilysins are present some of the alexins are destroyed and the bacteria are not all killed or weakened. Those remaining active are then further acted upon by the alexins in the tissues and by the substances given off by the leucocytes. If these protective substances are insufficient the infection is established.

According to Ehrlich the production of antitoxins and of the specific portion of bactericidal sera is due to overproduction of molecules in cells sensitive to the toxins or bacterial cell products. Ehrlich considers that toxin molecules have what he calls haptophore atom groups which find in sensitive animals cells and atom groups having for them an affinity. The groups unite and later the poison or toxophore atom group of the toxin molecule having been assimilated acts upon the vital part of the protoplasm of the cell, and injury results. This injured cell substance is replaced by the cell in excess, and this excess is thrown off free in the blood. This free cell substance has affinities similar to what it had in the cells and so unites with the toxin molecules, and satisfying them, neutralizes their poisonous properties.

When the substance of bacterial cells is injected into a susceptible animal body, there results in the same way as with toxins an injury of certain cell molecules, and an attempt at repair, with usually an overproduction. The specific substances produced cannot alone attack living bacterial cells similar to those whose protoplasm has previously caused the injury. To destroy the bacterial cell, besides the specific "antibody" there is needed a complementary body. This is the substance normally present in all healthy sera. The two substances together, uniting with the bacterial cell, destroy it.

According to Ehrlich these specific substances are present in minute amount in all living animals. After an injection or a series of injections, that one which has affinity for the poison or bacterial protoplasm is enormously increased. These atom groups of the large molecules of certain body cells are "side chains" as it were, which stand in the same relation as the side chains of the aromatic attachment to the benzol nucleus. On the ability of these groups to unite lies their tendency to be poisoned or to protect.

The agglutins seem to have a close resemblance to, if they are not identical with, the antibodies, which together with the complementary bodies destroy the bacteri

Ehrlich's "side-chain" theories are most interesting; whether they have in them a foundation of truth, or not, only further investigation can reveal. They have, however, helped greatly to establish that the protection given by antitoxic and bactericidal serums is due, for the most part at least, to purely chemical action, the antitoxins uniting with the toxins, and the bactericidal antibodies and complementary bodies combining with the bacterial cells.

An important fact recently established is that while we may accumulate antitoxin to almost any extent in the blood of infected animals, we cannot so increase the bactericidal substances in the serum, for the complementary body which is essential can never be increased in the blood much beyond the extent to which it is normally present in the blood. We can neutralize any amount of toxin by sufficient antitoxin, but we cannot protect an animal from death from a septicæmic germ, if we give an excessive quantity of bacteria. At the present time, therefore, we cannot be hopeful of having protective sera which will be of much value in the treatment of disease, when an extensive invasion of the body by bacteria has taken place.

With antitoxins we seem limited also to those cases in which we can give the antitoxin before sufficient toxin has united with the body cells to produce fatal injury. If even seven minutes have elapsed after an excessive amount of tetanus poison has been injected into a sensitive animal, no amount of antitoxin will protect it from death, while if previous to the injection of the toxin, the same amount of antitoxin has been mixed with it, no harm results.

The injection of toxins and bacterial poisons is followed after forty-eight to ninety-six hours by the development of protective substances. The immunity reaches its height a week or ten days after the injection, and then continues for a week or two, when it slowly declines again. When protective sera are injected the immunity is greatest at the time of the injection and then gradually lessens. The immunity following serum injections is frequently called passive immunity and that due to bacterial or toxin injections active immunity.

If a greater quantity of protective substance is desired in the blood than occurs after one infection, repeated injections of living or dead bacteria or their products are given, the doses being administered at short intervals and in sufficient amount to produce a slight elevation of temperature and malaise. Then, as soon as the animal returns to a normal condition, another injection of slightly greater quantity is given. After several months of such treatment the blood is withdrawn, allowed to clot, and the serum then siphoned off aseptically and stored either with or without the addition of preservatives. The serum is tested by mixing it with a certain number of times the fatal dose of a culture or its toxins whose virulence or toxicity is known, and then injecting this under the skin, in the vein, or into the peritoneum, according to the nature of the bacteria to be tested. The main point is that some definite method be carried out by which the relative value of the serum can be judged in comparison with other serums. As a rule, the value is stated in the number of fatal doses of culture or of toxin which a fraction of a cubic centimetre of serum will prevent from destroying the animal. It is well to remember that with a living germ a multiple of a fatal dose is not as much more severe than a single dose as the figure would suggest. One thousand times a fatal dose of a very virulent micro-organism will be neutralized by

several times the amount of serum which a single fatal dose requires, since in the case of very virulent living bacteria whose virulence is due to their ability to increase, it is not the organisms which are introduced that kill but the millions that develop from them. As a rule, the serum has to be given before the bacteria introduced into the body have multiplied greatly. After that period has elapsed the serum usually fails to act. The immunity conferred on a person from serum lasts from a few days to several months, according to the amount of serum injected. As in animals, it is strongest immediately after absorption. An injection of bacterial poisons or the contraction of actual disease usually confers immunity in from one to three weeks after the infection, which lasts, according to the nature of the infection, from one month to a year or more. The serum loses all appreciable protective value as measured in test animals in the usual doses before the person is liable to infection. Repeated injections of serum continue this condition of immunity indefinitely.

The use of sera having specific protective properties has been tried in both animals and man as a preventive of infection. In susceptible animals injections of some of the very virulent bacteria, as pneumococci, streptococci, typhoid bacilli, and cholera spirilla, can be robbed of all danger if small doses of their respective sera are given before the bacteria have increased to any great extent in the body. If given later they are ineffective. For some bacteria, such as tubercle bacilli, no serum has been obtained of sufficient power to prevent infection. Through sera, therefore, we can immunize against an infection, and even stop one just commencing; but as yet we cannot cure an infection which is already fully developed, though even here there is reason to believe that we may possibly prevent an invasion of the general system from a diseased organ as by the pneumococcus from an infected lung in pneumonia. On the whole, the sera which simply inhibit the growth of bacteria have not given, as observed in practice, conclusive evidence of great value in already developed disease. This is partly due to the difficulty of determining early enough the exact nature of the bacteria causing the infection. Although the serum of animals which have been infected with any one of many varieties of bacteria is usually both antitoxic and bactericidal, still one of these protective substances may be present almost alone; thus antitoxic substances are present almost exclusively in animals injected with two species of bacteria which produce powerful specific poisons—the bacilli, namely, of diphtheria and of tetanus. When the toxins of either of these are injected in small amounts the animals after complete recovery are able to bear a larger dose without deleterious effects, and these doses in the more suitable animals can be gradually increased until a thousand times a previously fatal dose may be administered without any serious results whatever. To Behring and Kitasato we owe the discovery that this protecting substance accumulates to such an extent in the blood that very small amounts of serum are sufficient to protect other animals from the effects of the toxin.

Some other important parasitic bacteria produce toxins and in the body antitoxins, but all to a far less extent than those of tetanus and diphtheria. Following them is the plague bacillus, and then, but far behind, the cholera spirilla, the typhoid bacilli, the streptococci, etc. These latter bacteria produce more of the substances which inhibit bacterial growth than of those which neutralize their toxins.

Inherited Immunity.—Natural immunity pertains more to species than individuals, and such immunity is handed down by the parents to their offspring. If the immunity of one or both parents has been acquired by them during their lifetime previous to the birth of the offspring the immunity conferred is slight or none at all. This is especially true of the male side. In the case of the female parent another factor comes into play after the fructification of the ovum,—viz., the absorption of products from the fluids of the mother, for the placenta is no barrier to soluble substances. Thus, sheep which have been immunized to anthrax have moderately immune young. On the other hand, animals vaccinated with cowpox have not been found to have immune offspring. Antitoxins injected into the parents apparently pass the placenta, giving thus a slight transitory passive immunity. A slight immunity is also given by immune mothers through their milk, a small amount of antitoxic substance being absorbed. *William H. Park.*

IMPETIGO.—This is an acute specific inflammatory affection of the skin, spontaneously and experimentally inoculable, contagious, and epidemic; characterized by the formation of superficial flaccid vesicles which soon rupture and give place to crusts formed by the drying of the effused serum. These crusts are without inflammatory areola and look as if stuck on the sound skin, the underlying epidermic erosions healing in a few days without leaving cicatrices.

Impetigo is a disease peculiar to infants and young children, not that there is with them any special underlying predisposing cause in the soil, so to speak, such as a strumous or lymphatic condition as is often alleged, but that simply their skins are more delicate, particularly that of the face, where the corneal epidermis is less thick and where impetigo occurs most frequently.

Given an erosion of the skin—and the thinner the skin the more easily does erosion occur—and the introduction of the special germ, a characteristic lesion of impetigo will result. The *accidental* causes which lead to this inoculation are those that conduce to scratching by which the skin is broken, such as phthiriasis, especially of the scalp, and scabies. Eczema may lead to impetigo. The contagiousness of impetigo was clinically established by Devergie and experimentally proven later by Tilbury Fox, of London, and others. Fox prefixed the term contagious, which would make it appear that his "contagious impetigo" was a different affection from the impetigo of the French school, which is not the case. Impetigo and "contagious impetigo" are one and the same disease and "contagious" is an entirely unnecessary and confusing qualification. Through the more or less intimate association with the greater opportunity for contagion that takes place in schools and families, impetigo may become epidemic solely through the inoculation of one by the other of the members of such bodies. The direct and efficient cause of impetigo is a microorganism—one of the streptococci.

The elementary lesion of impetigo is an erythematous spot but slightly if at all elevated, varying in size from the head of a large pin to that of a split pea. This lesion is very transitory and gives place in a few hours to a superficial flaccid vesicle containing a clear limpid serum. The thin corneal covering of this blister-like lesion is easily ruptured, spontaneously or by scratching, allowing to exude a limpid serum which quickly coagulates and forms the characteristic honey-like crusts that appear as if stuck on the sound skin. An accumulation of these friable amber-yellow crusts, without surrounding inflammatory areola, over the cheeks, forehead, and chin, and around the lips, presents a classical picture of the disease known as impetigo. It may occur on any part of the body, but the face is the familiar location. At times, after the breaking of the imperfect vesicle, little or no exudation will take place, so that no crusts are formed, there being merely a thin glaze over the underlying superficial erosion which heals quickly, leaving an erythematous spot that slowly disappears. This abortive attempt is noticed more frequently in grown persons. Ordinarily through successive reinoculations an attack of impetigo will last for from three to four weeks. The burning and itching, though slight, are sufficient in a child to cause it to scratch the lesions, thereby infecting the finger nails, and thus transference to other parts is effected with the establishment of new lesions. When uncomplicated, the lesion of impetigo never suppurates and terminates, after falling of the crust and the gradual

disappearance of the underlying reddened, area without cicatrix.

Impetigo may be diagnosed from varicella by the more widespread distribution of the latter, impetigo being essentially regional; the vesicle of varicella is smaller and more prominent, is surrounded by a wide area of erythema, and dries up into smaller and far less bulky crusts.

From ecthyma the diagnosis is made by the distribution of the lesions of the latter on the covered portions of the body, and by the greater intensity of the inflammatory process in ecthyma with accompanying indurated base, wide inflamed areola around the crust-covered pustule, and deeper erosive action upon the skin.

A bullous impetigo—a rare form—has at times been erroneously reported as "acute pemphigus in children."

A crusted impetigo lesion may simulate a syphilide, especially when situated around the mouth and chin in adults; if the lesion is one of syphilis the crust on being removed will be found to have surmounted a papule or a sanious ulcer.

Treatment is simple and effective. Removal of the crusts by soaking in olive oil until they are easily detached is the first step, after which an application, renewed twice daily, of a five- to ten-per-cent. ointment of ammoniated mercury will complete the healing in a few days, leaving only the after-redness which in turn gradually disappears. This treatment is all-sufficient, and while there are many other remedies that will perhaps cure as well, there is none better than this.

Charles Townshend Dade.

IMPOTENCE. See *Sexual Organs, Male, Affections of.*

IMPREGNATION is the union of two germ cells, to form a single new cell, capable of initiating by its own division a rapid succession of generations of descendent cells. This process is more frequently called *fertilization* or *fecundation*. The new cell is called the impregnated, or fertilized, ovum; also, especially in botany, it is called *oöspore* or *zygote*. The production of cells from it is called its segmentation, or cleavage. For the theory of the relation of the elements to one another and to other cells, see *Sex;* for accounts of the sexual bodies, see *Ovum* and *Spermatozoon*.

In all multicellular animals, impregnation is effected by three successive steps: 1, The bringing together of the egg and spermatozoon; 2, the entrance of the spermatozoon into the ovum, and formation of the sperm nucleus; 3, fusion of the sperm nucleus with that of the egg to form the segmentation nucleus. We proceed to consider these steps in their order.

1. The Bringing Together of the Germ Cells.—This is effected among animals in a great variety of ways, which, however, fall into two groups, according as the impregnation is effected, (*a*) outside the body of the mother, or (*b*) inside. The simplest manner is the discharge of the eggs and spermatozoa at the same time into the water, leaving their actual contact to chance, the method of the osseous fishes for the most part, and of many invertebrates. An advance is the copulation of the Anura (frogs, etc.), the male embraces the female, and as the latter discharges the ova, ejects the sperm upon them. In the higher vertebrates the seminal fluid is transferred from the male to the female passages during coitus. The physiology of this complicated function does not fall within the scope of this article.

For a long time it was not known how the semen fertilized the ova; the problem was long fruitful of fruitless speculation. The first step toward gaining actual knowledge was the discovery of the possibility of artificial fecundation by Jacobi, in 1764. Spallanzani was the first to take advantage of this, and to show that fecundation implied a material contact of the semen with the ova, and thus to set aside De Graaf's notion of the *aura seminalis*. But not until fifty years later did the memorable experiments of Prévost and Dumas (*Annales des Sciences Naturelles*, 1824) establish the fact that the spermatozoa are the essential factors of fertilization. Again, a little over fifty years later, Hertwig and Fol showed that one spermatozoon suffices to impregnate an ovum.

We have then to consider how the spermatozoa, after the semen has been transferred to the female, attain the ovum. They are found in mammals after copulation in the vagina and even in the uterus, but it is not clearly ascertained how they get beyond the vagina. It is probable that they travel through the female passages partly by the movements thereof, partly by their own locomotion, and enter the Fallopian tubes, though why or how is really unknown, and pass upward to meet the ovum. They are found in considerable numbers in the Fallopian tubes. The ovum meanwhile travels down the oviduct, it probably being impelled by peristaltic movements of the duct.

The meeting point or site of impregnation in placental mammals is about one-third, perhaps one-half way down from the fimbria to the uterus. It is remarkably constant for each species. Nothing positive is known as to the site of impregnation in man, but there is no reason to suppose, as is unfortunately often done, that the site is variable or different from that in other mammalia.

In the sexual reproduction of plants the germ cells are brought together in a great variety of ways; and in the higher forms the process is complicated by an alternation of generations. It will suffice for our present purpose to note that in many of the lower plants the male germ cell is an actively motile *spermatozoid*, homologous with the spermatozoon of animals, on the one hand, and with the germ cell of the pollen grain in higher plants, on the other hand.

2. The Entrance of the Spermatozoon into the Ovum and Formation of the Sperm Nucleus.—With our present knowledge, the assumption appears unavoidable that the ovum exerts a specific attraction upon spermatozoa of the same species. We observe, in fact, when artificial fecundation is employed, the spermatozoa swarming around the ova as if held by an irresistible impulse. This phenomenon occurs with every class of animals, even in mammals, whose freshly removed ova were examined on a warm stage under the microscope (Rein). Stassano has maintained that the eggs of echinoderms do exert such an attraction and also a similar but less strong attraction upon the spermatozoa of allied species. Since the brothers Hertwig have found by their experiments with sea urchins that hybrid impregnation takes place more readily after the ova have been kept awhile, Stassano's view involves the further assumption that the specific nature of the attraction fades away during a few hours. Very suggestive in this connection is Pfeffer's discovery that certain chemical substances may attract moving spores, etc., to definite spots. It is conceivable that the ovum may draw the spermatozoa toward itself by chemical influence, acting as an attracting stimulus. That this attraction may be exerted by the cytoplasm of the egg alone, is shown by the experiments of Boveri, Hertwig, Bresi, and Morgan, who found that spermatoza will enter enucleated fragments of eggs.

There may be mechanical devices to facilitate the entrance of the spermatozoon; this is, perhaps, generally true of all ova with micropyles serving for the passage of the spermatozoa. A careful study of such devices in the cockroach has been made by Dewitz, who found that the motions of the spermatozoa of this insect are peculiar, and adapted to increase the probability of their passing through one of the micropyles of the ovum. In ova without micropyles, among which those of mammals are included, the spermatozoa may, so far as we know, penetrate any part of the envelopes.

In the rabbit (Rein) about ten hours after coitus the ovum is found nearly half-way through the oviduct, and surrounded by many spermatozoa, perhaps a hundred, more or less. These are all, or nearly all, in active motion, for the most part pressing their heads against the zona radiata. Several of them make their way through into the interior of the zona. According to Hensen, only those spermatozoa which enter the zona along radial lines can make their way through; those which take