pharmaceutical business of his father, specimens of a urea apparatus and a urine-test case designed by him. The urea apparatus consists of a small wooden box containing two bottles, fitted with perforated rubber corks, connecting tubes, a graduated pipette, and a graduated measure. Two solutions are also supplied in the box ready to mix to make up the hypobromite fluid. The whole forms an apparatus for the quantitative estimation of urea in urine. In practice, the nitrogen liberated by the hypobromite displaces the water in one of the bottles, the quantity of water so displaced is measured, and the volumes of nitrogen and water being equivalent, the quantity of water displaced forms a measure of nitrogen evolved. From this the calculation of the percentage of urea is easy, and a table on an enclosed card shows at a glance the equivalents in grains per ounce and per pint. Very little practice will enable any one to perform the estimation with this apparatus, and we have found that in working, the margin of error is not more than 2 per cent. of the correct result. The urine-test case is exceedingly ingenious and well contrived; it contains the requisite apparatus for ordinary urine testing in a very compact form. The box measures 6 by 3 by $4\frac{1}{2}$ in., and comprises two bottles of solutions for Fehling's fluid, a bottle of Esbach's picric acid test, and another of hypobromite. There are four test tubes in a "nest;" one is graduated as the ordinary Esbach's tube and also for the quantitative estimation of urea, which is performed by fitting in a bulb with ground-glass junction, and using it in the same way as Doremus's ureometer. The box also includes a graduated pipette for this purpose. The other articles are a spirit lamp, urinometer, glass funnel, packet of filter papers, some broken glass (for use in the boiling tube to prevent "bumping"), and last but not least, a cloth for drying and cleansing. It will be seen from this enumeration that the adjectives "ingenious and well contrived" are justified. On the lid is pasted a table of the equivalents for the estimations of sugar and urea. The price is not extravagant. The apparatus can be obtained from Mr. W. H. Martindale, 10, New Cavendish Street, London, W.

Southey's Capillary Drainage Tubes.—Dr. T. GARRETT HORDER (Cardiff) writes: I daresay other surgeons have experienced, like myself, some difficulty in fixing the tubing on Southey's capillary drainage cannulas, and it may interest such to know that Mr. Stainforth, of Cardiff, has, at my suggestion, made a pair of forceps which makes the fixing of the tubing an easy matter. The forceps have the ends bent over at right angles, and I am convinced that the invention is worth the attention of surgeons who are in the habit of using Southey's trocar.

SANITARY APPLIANCES.

A Sanitary Paper.—We have received from the Toilet Novelties Company, Bristol, some specimens of what they call "toilet requisites." The chief novelty is the so called toilet pocket book; this consists of a small bundle of thin paper, such as is ordinarily supplied in waterclosets, fixed by a simple and ingenious contrivance in a stout coloured paper cover, so that the whole looks like a pocket book. The paper appears to be of good quality. As the books lie flat and occupy but little space, and as they are inexpensive, they will probably be found useful, especially for travellers. There is a larger size, price 4d., containing sheets of thin paper, which the makers suggest might be used as handkerchiefs. Sir Rutherford Alcock, in his book on Japan published a good many years ago, said that the Japanese were horrified at the European plan of carrying linen pocket handkerchiefs which were returned to the pocket after use; they, he said, would as soon think of returning a paper handkerchief soiled with nasal secretions to their pocket, as they would paper which had been used for another purpose. At the present time, when influenza is rife, we are inclined to think that the use of such paper handkerchiefs, which could be immediately burned in the fire, would be a simple precaution well worth taking. The same company supplies a larger handkerchief of tough semi-transparent ornamental paper, very like the Japanese napkins which may be seen in some restaurants. These are quite cheap—2s. 6d. per 100—and may be recommended to persons suffering from any form of infective catarrh.

A SUMMARY AND ANALYSIS OF RECENT OBSERVATIONS AND THEORIES

AS TO

THE PROCESSES OF INFECTION AND PROTECTION IN THE ORGANISM.

By H. W. ARMIT, M.R.C.S.Eng., L.R.C.P.Lond.,

I.—OLDER THEORIES OF IMMUNITY.

Older Theories.

No time need be wasted on the consideration of the theories put forward at the period when the disease germ was believed only to be capable of existing in a "suitable nidus," for they carry no conviction with them, and on careful examination it will be found that they merely consist of the changing of one set of vague terms into another.

Some infective processes (for example, scarlatina, diphtheria, measles), are characterized by an incubation period, a prodromal stage, a stage of acute illness of varying length, and in non-fatal cases, a spontaneous recovery. In others the course of the acute illness is of a definite length (for example, typhoid fever, pneumonia), while others do not tend to spontaneous recovery. Why do some of these diseases spontaneously come to an end? What is the meaning of the incubation period? Again, we frequently observe that some diseases are communicated to only certain individuals and not to others. This is believed to depend on individual predisposition. In other cases nearly all those who come into the range of infection acquire the disease, which occurrence is said to depend on racial predisposition. Again, certain diseases may protect the individual attacked against a subsequent infection. How can individual and racial predisposition and natural and acquired immunity be explained? To understand the processes lying at the bottom of the phenomena an exact knowledge of the nature of infection is necessary, and therefore to the questions to be answered must be added: in what way does a micro-organism gain a foothold in the tissues, and how does it exert its toxic effects?

Natural and Acquired Immunity.

Natural immunity was taken as a starting point from which the study of these problems was attempted, and as a typical example of this the insusceptibility of Algerian sheep to anthrax as compared with the susceptibility of ordinary sheep to this disease, and the absolute immunity of dogs towards tetanus, may be instanced. Pasteur noted that a non-fatal attack of fowl cholera was followed by complete or partial immunity in proportion to the severity of the attack, and, by keeping cultures of the virus for a considerable time before inoculation, he obtained an attenuated form, so that the disturbance produced by inoculation was slight, but nevertheless the immunity acquired was for the time absolute. He believed that the attenuation was due to the oxidation of the microbe or its products, but Chauveau showed that it was due to the effect of temperature, and that cultures could be attenuated by heating to 42°C . in a short space of time, even in the absence of oxygen. The subject was considerably widened by the discovery of antitoxin by Behring. Salmon had previously shown that immunity might be produced by injecting the toxic products of bacteria freed from the bacteria themselves. Pasteur's explanation of immunity, in special reference to his anti-rabies inoculation experiments, was that side by side with the growth of the microbe a chemical substance was produced which arrested the development of the micro-organism. This substance would be a secretion product of the microbe, and it would be conceivable that if it were deposited in the organism it could be of use to prevent a future infection; but to explain natural immunity on this theory it had to be supposed that the substance might be normally present in certain individuals. This theory was unsatisfactory and others were formulated. In one the bacteria were supposed to use up the store of substances necessary for their existence, and that fresh injection was impossible from the lack of nutrient material; in another the action of the living cells was supposed to offer resistance to the growth of a micro-organism, which varied in different organisms and

towards different germs. In support of this theory, Kanthack¹ pointed out that every organism has special cellular mechanisms to ward off an infection. He instanced the fact that the acidity and proper supply of gastric juice proved in some cases too strong for the cholera vibrio, and quoted from Loeffler's experiments on the epithelial resistance against diphtheria, and from Orth and Wyssokowitsch, who showed that traumatic lesions destroyed this resistance of the cells towards certain infective processes. That these theories are not satisfactory is evident, but that they contain some germs of truth will be apparent from what is said later on.

Phagocytosis and Paraplasma Action.

Two other theories have next to be considered.

The first was the result of Ehrlich's study of the chemical changes of the cells. He² found that the protoplasm of the cell is a body which contains no free oxygen, and the paraplasma of the cell is a body which carries oxygen. Micro-organisms which require oxygen (aërobic) can exist in paraplasma, but must suffocate when they find themselves in true protoplasm. He suggested that certain forms of immunity might be explained by supposing that the protoplasm has the property, acquired by practice, of quickly taking up certain bacteria in itself, which have found their way into the paraplasma.

The other theory, which is better known chiefly because it is supported by visible biological rather than chemical changes (although Ehrlich rendered the latter visible with the aid of his colour reactions) is that of Metchnikoff, and is known as the "phagocytosis theory." Certain white blood corpuscles (polynuclear leucocytes) are endowed with the property of attacking, incorporating, and finally destroying certain bacteria, for example, anthrax bacilli. Metchnikoff did not explain how the phagocytes succeeded in killing the bacteria. The latter are supposed to exert a special action on the phagocytes, either attracting them "positive chemiotaxis" or repelling them "negative chemiotaxis." It must be assumed that in natural or acquired immunity there is positive chemiotaxis, and the phagocytes, being called into close contact with the bacteria, are then able to perform their special function. In order to explain the reason of this positive chemiotaxis, Roux has suggested that some forms of toxins are at times capable of converting the natural negative chemiotaxis into a positive chemiotaxis. There is reason to believe that the action of the polynuclear leucocytes (as phagocytes) has but little to do with the production of actual immunity, although they probably do play a part in assisting to protect the body against local infection. The position of Metchnikoff's theory in the protective regulations of the organism appears to be that of a temporary hindrance to the micro-organisms seeking to infect the body, acting during the early period before the more complex and more powerful neutralization regulations have come into play.

THE SIDE CHAIN THEORY.

It may be accepted as proved, without further argument, that bacteria gain a foothold at the chemical expense of the body organism, that they produce a chemical product which acts harmfully toward the organism, and that a second chemical product appears during the infection which suffices in some cases to neutralize the harmful products of the bacteria or to destroy the bacteria, or both. The second product, if stored up in the organism, will protect against a further infection. The chemical products of the bacteria are responsible for the symptoms of the disease, although a minor part is at times played by the mechanical effect of the bacteria. The method of action of the bacterial product or toxin has been worked out by many observers, and is now known to be analogous to that of the enzymes. E. Fischer³ has shown that toxins are unstable ferment-like bodies which possess a peculiar chemical constitution, having a configuration which renders them easily bound (in the sense of a true chemical reaction) to the proteids. The descriptions toxalbumen, toxoglobulin, etc., are only to be accepted for the substances made up of toxin bound to albumen, globulin, etc., and there fore ready for action. Between the molecules of the highly-

organized organic compounds of the body cells (protoplasmic molecules) and the toxins there exists a specific affinity which is of a selective character. Ehrlich⁴ has shown that this selective affinity is comparable to that of certain acids to alkalis. If to a mixture of hydrochloric acid and acetic acid an alkali is gradually added, it will be found that the hydrochloric acid is first completely neutralized before the acetic acid is attacked, so that a selective affinity exists between the hydrochloric acid and the alkali, which is stronger than the affinity which exists between the acetic acid and the alkali. This affinity, the firm permanent binding of the ferment-like body to the protoplasm, the difference between the behaviour of the toxins and of defined chemical bodies, such as alkaloids, and the bio-chemical action of the fixed body led Ehrlich to formulate in 1897 his "side-chain theory." This theory depends on the assumption that the complex molecule of the protoplasm is a compound structure like other organic chemical bodies, consisting of a central radical and groups of more or less complex nature attached in such a manner that these lateral groups or side chains are capable of combining with other formed chemical bodies, or of being replaced by other complexes. That an analogous process occurs in organic chemistry is generally accepted to explain the relations of isomeric compounds and the various series of carbon compounds. The formulae for butyl alcohol—normal, secondary, and tertiary—have been expressed thus:

Ehrlich contends that the protoplasmic molecule is capable of forming a vast number of various side chains, and that a separate chain can be formed for every blood or cell poison which exists. The nutrition molecule is attached to the normal side chains. To the objection that the number of side chains would have to be very large, it is replied that there are many conditions in Nature in which a large number of chemical bodies or offshoots arise, even from a simple structure. Ehrlich points out that from the cells of the cinchonaceae, at least twenty different alkaloids can be obtained. The protoplasmic molecule he suggests forms a large variety of these side chains or "receptors," and each receptor is capable of anchoring one single body, be it albumen, peptone, toxin, or other body. The atom arrangement, or group in the toxin, which corresponds to the receptor, he calls the "haptophoric group." The toxin molecule, however, must consist of more than a simple arrangement with one atom group, for he found that certain conditions modified the toxin, suspending its toxic action, without disturbing its power of attachment to the protoplasmic molecule. The toxin molecule therefore must possess a second group which he calls the "toxophoric group," through which the physiological function of the toxin acts. The modified toxin⁵ consists of a molecule with a haptophoric but no toxophoric group, and is called "toxoid." The evidence of the existence of these groups will be dealt with later on.

Before following the chemistry of the toxin further, it may be as well to turn to one of the questions, namely, "What is the meaning of the incubation period?" and to formulate the reply according to the side chain theory. The process which has to be gone through after infection consists in the manufacture of toxin, the carrying of it off, the attracting of suitable receptors of sufficient affinity to its haptophoric groups, and lastly the acting of the toxophoric group, through the

¹ Kanthack, *Contagion, Infection, and Predisposition*, 1892.

² Ehrlich, *Die Sauerstoffbedürfnisse des Organismus*, 1885.

³ Pfeiffer, *Deut. med. Woch.*, 1896, Nos. 7 and 8.

⁴ Ehrlich, *Ueber Toxine und Antitoxine, Therap. der Gegenart.*, 1901.

⁵ Compare the attenuation of Pasteur.

toxin molecule to the protoplasmic molecule, which is evidenced by a definite defect in the molecule. This process must occupy some time, especially if one considers that the toxophoric group possesses a ferment-like action. The haptophoric group possesses a great affinity to the receptor, so that but little of the incubation period is used by the anchoring of these two, but the slow action of the toxophoric group has to answer chiefly for the loss of time.

Effect on the Cell.

The effect of the anchoring of the toxin molecule to the cell molecule is ascertained to be a defect in the molecule. The receptor is no longer capable of receiving nutrient molecules; and, therefore, not only its own nutrition but also its function as a carrier of nutrient material is interfered with. The amount of damage done to the cell varies according to the quantity of activity exercised by the toxophoric group. If the action is small at first, and is gradually increased, the result is a stimulation of the molecule to throw out more receptors of the same type, which will not only compensate the defect but may even over-compensate it. The excess of newly-formed receptors is unnecessary for the molecule. They are therefore cast off. They retain, however, their affinity for the toxin molecule, but cannot be reattached to the cell molecule. When toxin is now introduced into the organism it is anchored by the free receptors, and thus prevented from being bound to the cell. *These cast-off receptors are what is known as antitoxin.*

The products of the bacteria will therefore, under most circumstances, be neutralized after the cell molecule has passed through the stages of reproduction, compensation, overcompensation, and casting off, in reply to the stimulation caused by the initial defect, and antitoxin will result. It would be difficult to explain in this way the secondary or late symptoms of certain diseases (for example, diphtheritic paralysis), without the help of a further regulation. Ehrlich⁶ Madsen, and others have shown that a variation of bacterial products occurs, which acts much more slowly on the cell molecule, and which, therefore, does not call forth any overproduction of receptors for a considerable period of time. Ehrlich has named this variety "toxox." He claims, however, that the haptophoric groups of toxox are identical with those of toxin, since he says they are entirely covered by the introduction of normal antitoxin. This is open to criticism. The injection of diphtheria antitoxin does not prevent the occurrence of post-diphtheritic paralysis, and this, I believe, is due to the haptophoric groups being incapable of combining with the thrown-off receptors, produced in the covering of the cell defect which has been caused by toxin. If this were not so, then early injections of normal antitoxin would prevent a very marked effect of toxox on the cells of the nervous system in most cases. As a rule, this does not occur.

Mode of Destruction of the Bacteria.

It appears that the bacteria, having gained an entrance into the body, seek a suitable resting place. Aërobie germs find this in paraplasmic tissue, and anaërobie germs in protoplasmic tissue. Once safely ensconced (they have only to evade the action of the phagocytes), they behave in exactly the same manner as they do when artificially grown on nutrient media, forming colonies. The natural length of life of any one bacterium, bacillus, or coccus is probably the same inside the body as in the culture tube, and the process of multiplication is certainly carried on in the same manner. The bacteria produce toxin and toxox by a process of secretion, which varies with certain species within narrow limits. An interesting observation has been made by Bulloch and others, that the toxin of the tubercle mycobacterium is contained in the bodies of the bacteria, and probably is not carried out into the blood or lymph streams until the particular micro-organism has finished its career, has produced its share of the succeeding generation, has died and become disintegrated. In this case a wholesale destruction of the bacteria without an accompanying protection of the organism by antitoxin would inevitably lead to the death of the host.

(To be continued.)

THE PREVENTION OF CONSUMPTION.

AUSTRIA.

The Imperial Royal Medical Society of Vienna has appointed a committee for the study of the tuberculosis question. The Committee includes, in addition to several other members, Professors Benedikt, Gruber, Monti, Mosetig, Neumann, Neusser, and Nothnagel.

BELGIUM.

The King of the Belgians has asked a well known architect to submit to him a design for a sanatorium for tuberculous patients which he intends to build on his estate of Passable, near Saint Jean-sur-Mer. The sanatorium is intended for the reception of Belgian subjects.

ITALY.

The Directing Council of the Association for the Prevention of Tuberculosis at Milan has recently adopted resolutions to the following effect:

1. To take steps to make the propaganda against tuberculosis more active among the working classes.
2. To distribute as widely as possible among the people cards inscribed with the words "Do not spit on the ground."
3. To appoint a committee consisting of Professor Bertazzoli, Dr. Massaglia and others, to approach Cardinal Ferrari, to request him to ask parish priests to allow these cards to be posted up in their churches, and to impress on their flocks from the pulpit the duty of taking the necessary hygienic precautions against the dissemination of tuberculous infection.

UNITED STATES.

A Bill for the creation of a tuberculosis commission in Maryland is likely to pass the General Assembly without opposition. The commission is to be appointed by the Governor, and is to consist of five members, of whom three are to be physicians. All institutions having medical officers, and supported in whole or in part by the State, are required to furnish the commission certain kinds of information concerning tuberculosis. The commission will be given powers for two years, after which it will cease to exist unless it is given a fresh lease of life by the Legislature.

THE PLAGUE.

PREVALENCE OF THE DISEASE.

INDIA.

The deaths from plague in India during the week ending March 1st reached the enormous total of 21,789. Compared with the previous week, when they numbered 14,946, the increase is very great, and still more marked is it when compared with the corresponding week in 1901, when the number was 6,901. The chief increase is in the Punjab, where 10,525 persons died of plague during the week ending March 1st.

In the towns and districts of India chiefly afflicted the deaths from plague during the week ending March 1st were:—In Bombay City 750, against 701 during the previous week; Bombay districts 5,203, against 4,373; Calcutta 349, against 176; Bengal 1,101, against 863; North-West Provinces and Oudh 2,143, against 1,351; Punjab 10,525, against 5,922; Kashmir (Jammu) 330, against 317; Madras Presidency 456, against 543; Mysore State 426, against 507.

It will be observed that in the more southerly parts of India the plague mortality is lessening, whereas in the north the figures are larger in every instance. In the Punjab, the most seriously affected districts are Jullundur, where 808 deaths from plague occurred; Hoshiarpore with 808; Gurdaspore 570; Sialkot 1,850; Ludhiana 63; Ferozpoore 294; Umballa 1,622; Patiala State 1,510; Kemultola 63; Nabha 525; Bahawalpore 21; and Patiala City 175. At Karachi the plague shows signs of increasing, and at Hyderabad (Sind) as many as 52 deaths from plague occurred on February 28th, and 44 on March 1st.

In Calcutta, during the four weeks ending March 15th 1,488 persons died of plague.

CAPE OF GOOD HOPE.

On March 1st but 1 case of plague remained under treatment in the Plague Hospital of Cape Colony. There were no fresh cases nor any deaths from the disease during the week ending March 1st in any district of the Cape.

MAURITIUS.

During the week ending March 26th, 6 fresh cases of plague were reported in Mauritius and 3 deaths from the disease.

THE FUND FOR THE FAMILY OF THE LATE DR. WILLIAM SMYTH.

DR. CALWELL, 1, College Square North, Belfast, Honorary Secretary of this fund, begs to acknowledge the following late subscriptions:

	£	s.	d.
Dr. A. W. Esler, Victoria, Australia	...	...	...
Dr. W. S. Ross (per Dr. Whittla), Wairarapa, New Zealand	...	...	...
Captain E. B. Barnett (per Messrs. Holt and Co., London)	...	...	...

⁶ Ehrlich, Werthbestimmungen des Diphtherieheilserum, *Klin. Jahrb.*, 1897.