THE CROONIAN LECTURES

ON THE RELATIONSHIP BETWEEN

CHEMICAL STRUCTURE

AND

PHYSIOLOGICAL ACTION.

Delivered before the Royal College of Physicians of London.

By T. LAUDER BRUNTON, M.D., D.Sc. EDIN., LL.D. ABER., F.R.S.

Fellow of the Royal College of Physicians; Assistant-Physician and Lecturer on Materia Medica at St. Bartholomew's Hospital.

LECTURE II.

EXPLANATION OF THE DANGER OF DISEASED MEAT.

Some very interesting experiments by Bocklisch may perhaps explain this rarity of ptomaine poisoning. In experimenting with pure cultivations of the vibrio proteus, better known as "Finkler's bacillus," he found that it did not seem to produce any poisonous substances, although it occurs in the dejecta of patients who have been suffering from sporadic cholera, and is supposed to cause the disease. It occurred to him, however, that it is never present in the human intestine as a pure cultivation, and that possibly the presence of another bacillus along with it might cause the formation of the poisonous products in sporadic cholera. He therefore mixed some other putrefactive bacteria with it, and found that the mixed bacilli formed the highly poisonous substance, methylguanidine.

In the same way, it seemed not unlikely that cases of acute poisoning by meat or game may be due to the accidental presence of more than one kind of bacillus, leading to the formation of specially poisonous products. More especially is this likely to be the case if one of them is a pathogenic microbe which has already produced disease in the beast or bird yielding the meat and a certain amount of decomposition of its tissues before its death.

IMPORTANCE OF FERMENTS AND PRODUCTS OF ALBUMINOUS FERMENTATION IN RELATION TO POISONING AND DISEASES.

Decomposition of Albumin.—Albuminous substances are of a very complex composition, and contain a huge number of atoms. In the process of decomposition by heat, as in burning or dry distillation, by putrefaction, or by the action of enzymes such as pepsin or trypsin, the large molecule of albumen becomes decomposed, yielding simpler and simpler substances. The huge albuminous molecule will not diffuse through vegetable parchment. The final products of its decomposition, such as compound ammonias and organic acids, diffuse readily. Between these two stages we find intermediate substances—albumoses and peptones.

Albumoses and Peptones.—Albumoses and peptones are amongst the products of normal digestion, but they are now acquiring a special interest from the discovery that, when introduced into the blood without passing through the liver, these digestive products may act as powerful poisons.

Albuminous Substances as Food and Poison.—It seems strange that food and poison should be so nearly allied, and that, while albuminous substances are indispensable for the maintenance of life, the substance into which they must be broken up before they can be assimilated will kill an animal if they are applied in a wrong way and are injected into the jugular vein instead of being absorbed from the intestine in passing through the liver. But a house is very necessary for people to live in, and, if it has to be transferred from one place to another it may be occasionally, as in Chicago, mounted on rollers and moved on; but in this country, we generally pull it down and rebuild it. In this process, as Hermann has well put it, we separate the bricks from one another, and then put them together again. The bricks are quite harmless, and are very useful when properly applied to building the house, but a brick may be a fatal weapon if it is misapplied by being flung at a man's head. The albumoses and peptones into which albumins split up in the process of digestion are much more readily absorbed than the albumins themselves would be, and when they are put together again in the proper way in the portal vein or liver they support the strength, maintain life, and do no harm, but only good, to the organism.

Poisonous Albumins—Fibrinogen.—Most of us, no doubt, have eaten and enjoyed sweetbreads, which sometimes consist of the pancreas and sometimes of the thymus gland of the ox, and have received nothing but pleasure and strength from doing so; but it has been shown by the gifted young physiologist and pathologist whose recent untimely death has been such a blow not only to his friends, but to scientific men throughout the world, Dr. Wooldridge, that the juice of the thymus gland, if injected into the veins of a rabbit, will cause almost instantaneous clotting of the blood throughout the body, so that a small quantity of this albuminous juice, containing a kind of fibrinogen, kills the animal as quickly as a toxic dose of hydrocyanic acid or a bullet through its head.

Poisonous Digestive Products—Albumoses and Peptones.—The albumoses and peptones formed during digestion seem to have just the opposite action. They prevent coagulation altogether, and produce coma, convulsions, and death.

Serpent Venom—Jequirity.—Moreover, the venom of serpents has been shown by Weir Mitchell, Reichert, and others to belong, in part at least, to this class of substances, and some vegetable poisons do so also, for in a most interesting research Martin has shown the jequirity poison also to be an albumose. The poisonous action of albumoses is destroyed by boiling, and as the venom of the cobra is weakened but not completely destroyed by boiling, it is probable that it does not consist entirely of an albumose, but contains some other poisonous substance as well.

Diphtheritic Poison.—The interesting point in the relation of ferments or albumoses to disease is that the poisons formed by some disease-germs belong to this class. Thus Roux and Yersin have found that the poison of diphtheria has its virulence completely destroyed by boiling, just in the same way as the poison of the jequirity seed.

Products of more complete Decomposition of Albumin, Alkaloids, Ammonia.—But as albuminous molecules become more broken up, the products of their decomposition no longer have their poisonous properties destroyed by heat. I may perhaps again be allowed to use a simile which I have employed on a former occasion¹ and liken the food we eat to the utensils which we use. A plate or a tumbler although it might, like the brick, occasionally be awkward if used as a missile, can hardly be called dangerous; but when broken or splintered the fragments may cut or pierce, or inflict serious or even deadly injuries. If the fragments are large they can easily be cemented into a whole utensil, and thus be deprived of their injurious character. In like manner albumoses and peptones are built up into non-poisonous albuminous substances in the liver and portal vein. If the splinters are smaller it will be difficult or impossible to do this; and the ptomaines or alkaloidal substances resulting from the further decomposition of albumin may not undergo synthesis in the portal system, but pass through the liver, and act as poisons in the general circulation. But if we break these splinters by pounding them into fine dust, we may again make them almost completely harmless, and in the same way the final products of albuminous decomposition, ammonia and carbonic acid, have but a very slight poisonous action, and only kill when used in very large quantities, while the ptomaines, which may be likened to the splinters, are very deadly.

Ptomaines and Leucomaines.—The alkaloids formed by the decomposition of albumin in the dead body are termed "ptomaines," while those which are formed in the living body have received the name of "leucomaines."

NATURE OF PTOMAINES.

The chemical constitution of all the ptomaines has not been ascertained, but a number of them seem to be compound ammonias. If one happens to be passing through a fishing village at certain times of the year, one may notice a peculiarly pungent, disagreeable smell from herring barrels. This smell is due to the substance, trimethylamine, a substance which some years ago was recommended as a cure for rheumatism. It consists chemically of ammonia, in which 3 atoms of hydrogen have been replaced by 3 of methyl; thus:

Ammonia.

Trimethylamine.

This substance is one of the products of decomposition of albu-

¹ *Disorders of Digestion*, p. 277. London: Macmillan and Co.

minous substances, and has been found by Brieger in rotten cheese, and also in the cadaver.

A similar substance, dimethylamine, in which only 2 atoms of hydrogen are replaced, is found in decomposing glue; but these substances, though poisonous to frogs, have little toxic power in mammals, and are of little importance in connection with poisoning.

Ammonia and Ammonium.—I have already mentioned that nitrogen, although generally trivalent, is sometimes pentavalent, and, while we write NH_3 as the formula of ammoniacal gas, the formula of ammonium chloride is NH_4Cl .

The hydrochloric acid, HCl , attaches itself directly to the ammonia or to the compound ammonias in which the hydrogen has been replaced by radicals. In the case of the ammonia itself, we assume that a hypothetical substance, ammonium (NH_4), has been formed which behaves like the alkaline metals potassium and sodium. Consequently we term the compound thus formed ammonium chloride, as it corresponds to sodium chloride; but where we do not know the nature of the compound ammonia as in some of the organic alkaloids like morphine, we term the compound hydrochlorate.

It is generally believed that a similar change from trivalent to pentavalent nitrogen occurs when ammoniacal gas is dissolved in water. It then combines with the water, the latter splitting up, and one atom of hydrogen combining directly with the nitrogen, while the remaining OH becomes attached by its oxygen to the nitrogen, thus:

Some of the most important ptomaines are built of this latter type, namely, that of ammonium hydroxide. In them the 4 atoms of H are replaced by radicals, but they retain the hydroxyl (OH).

Formation of Ptomaines.—A glance at the accompanying table will show that three of the commonest (namely, neurine, choline, and muscarine) may be formed from trimethylamine, and alkyl radicals, in the same way as caustic ammonia is formed from ammoniacal gas and water.²

An atom of hydroxyl passes from the alkyl to the nitrogen of the trimethylamine, and the residue also becomes attached to the nitrogen. Choline was first prepared from bile, and hence its name, but it may also be obtained easily from yolk of egg. In small doses it has no poisonous action. In large doses it has somewhat the same effect as neurine, but the lethal dose is ten times as great.

COMPARISON OF CHOLINE, NEURINE, AND MUSCARINE.

Choline, neurine, and muscarine resemble one another very much in action, though varying enormously in their toxic power, muscarine being very much more powerful; possibly, also, though this point is not at all settled, choline and neurine have a certain tendency to paralyse the motor nerves and muscles in somewhat

the same way as curare, although this is not sufficient to interfere greatly with their other actions.³

ACTION OF CHOLINE, NEURINE, AND MUSCARINE.

The effect produced by all three bodies may be shortly referred to one property, namely, their power of irritating the peripheral extremities of nerves going to secreting cells or to involuntary muscular fibres. By stimulation of the ends of the nerves going to glands they cause salivation, sweating, lachrymation, and increased secretion of the pancreas, liver, and mucous glands.

By irritation of the motor nerves going to involuntary muscular fibres they cause these muscles throughout the body to pass into a state of violent contraction, the pupil becomes contracted, and there is disturbance of vision, with spasm of accommodation; cramp-like spasms of the stomach and intestine occur, and cause vomiting and purging, and there is contraction of the bladder, spleen, and probably of the uterus. To this condition of increased contraction the heart forms a marked exception, because the cardiac branches of the vagus nerve contain inhibitory as well as accelerating fibres, and strong irritation of the vagus nerve produces slow action or complete stoppage of the heart. At first muscarine causes slight quickening of the pulse and flushing of the face, but this is soon followed by slowness, and in frogs the irritation of the vagus is so great that the heart will remain motionless in diastole for hours.

The respiration is embarrassed, and sometimes oedema of the lungs may ensue. This is ascribed by von Basch to the disturbance of the cardiac action, but I am still inclined to think that contraction of the pulmonary vessels may be one factor in the respiratory embarrassment.

Antagonism of Atropine to these Alkaloids.—All the symptoms, whether produced by choline, neurine, or muscarine, can be rapidly and completely removed by atropine, which paralyzes the identical nervous structures which are irritated by muscarine.

Relation between their Chemical Constitution and Physiological Action.—From looking at the chemical constitution of those alkaloids, one might imagine that they owed their poisonous activity to the hydroxyl group, but this is not the case, because two other substances, similar in constitution, but without the hydroxyl, produce similar effects to muscarine,⁴ with the exception that they hardly contract the pupil at all.

These are:

And:

Valeryltrimethyl ammonium chloride.

What is most peculiar, however, is that hexyltrimethyl ammonium chloride does not act like muscarine either on the heart or intestine.⁵

Relation of Ammonia to the Liver.—It is interesting to note that the ptomaines I have already mentioned are substituted ammonias, because, as we shall afterwards see, ammonia and some of its compounds have a very remarkable action upon the liver.

AROMATIC PTOMAINES.

You will have noticed that none of the poisons I have just mentioned contain any radicals of the aromatic group. But other ptomaines do; indeed, the one which was first isolated by Nencki was collidine, which, like the others, contains three atoms of methyl, but associated with an aromatic nucleus.

³ Neurine also produces fever in rabbits (Otto and Colmar, *Journ. of Phys.*, vol. viii, p. 218). I do not know whether the other substances do so or not, nor whether atropine prevents neurine from raising the temperature.

⁴ Schmiedeberg and Harnack, *Arch. f. exp. Path. u. Pharm.*, Bd. vi, p. 112.
⁵ Jordan (in Schmiedeberg's Laboratory), *Arch. f. exp. Path. u. Pharm.*, Bd. viii, pp. 16 and 30.

² Armstrong, *Journal of Chemical Industry*, July 30th, 1887.

Another most important ptomaine appears also to belong to the aromatic series, for Vaughan thinks that the poisonous alkaloid of milk and cheese, which he discovered and named tyrotoxin, is really butyrate of di-azo-benzene. The symptoms produced

Di-azo-benzene butyrate.

by this alkaloid, which sometimes forms in milk during hot weather, are nausea, vomiting, headache, quick pulse, laboured breathing, constipation, and great prostration, with stupor. The pupils may be somewhat dilated, though not so much as in poisoning by atropine, and there may be also a scarlatina-like rash on the skin.

PRACTICAL BEARINGS OF OUR KNOWLEDGE OF PTOMAINES.

High Game.—The practical outcome of the facts I have just brought before you is that there may be very great danger indeed of poisoning by alkaloidal substances formed in meat by its decomposition. Yet we know that while tainted beef is strongly objected to, high venison is looked upon as a delicacy, and the experiments of Bocklisch indicate that very probably the presence of two kinds of bacteria may be the cause of poisons being formed.

Tainted Meat.—Tracing the question a step farther, we ask: How are the two kinds of microbes likely to be present? And the simplest explanation is that the dangerous meat may have been got from a diseased animal, and the microbes present in its tissues may, by combining their action with that of ordinary putrefactive bacilli, have caused the formation of the deadly poisons. If this should be found to be the fact, it will clearly explain the necessity of avoiding as unfit for use the flesh of animals suffering even from the very earliest stage of acute disease.

Atropine as a Possible Antidote.—The fact that choline, neurine, and muscarine are amongst the commonest products of putrefaction indicates the advisability of employing atropine as a remedy in these cases of poisoning where the symptoms resemble those produced by these three bodies, and we may hope that ere long the risk of poisoning by milk or cheese may be lessened by an antidote to the tyrotoxin being found, for a knowledge of its chemical nature indicates to us the direction in which an antidote is to be sought.

ACTION OF MICROBES IN THE INTESTINE.

Having considered the relation between disease and microbes living outside the body, we now come to discuss their action when they are taken into the intestinal canal, or applied to some absorbing surface such as that of a wound.

Microbes in the Intestine.—Bacteria abound in the intestine even in health, and some have thought that they might even aid the digestive juices in breaking up the food. It is quite likely that they aid in breaking up the food, but whether they do so with any advantage to the organism may be somewhat questionable. They tend to split up the products of pancreatic digestion farther than the pancreatic ferment would, and one of the substances to which they give rise is indol. This body has an antiseptic action, and belongs to the aromatic series, members of which, as I shall afterwards have to show, have a very marked action upon the liver. In the intestine it becomes converted into indican which is absorbed and excreted in the urine.

Indican in the Urine.—When the quantity excreted is excessive it indicates that albuminous matters are undergoing rapid decomposition. Unless there is some other locality where such a process is going on, as in an abscess, it usually indicates that bacteria are active in the small intestine and, rightly or wrongly, I am accustomed to look upon much indican in the urine as an indication for a mercurial purgative, mercury being one of the most powerful antiseptics we possess.

Poisons formed during Digestion.—The presence of bacteria is not necessary for the production of poisonous alkaloids in the intestine, for fibrin digested with pepsin yields a substance to which its discoverer, Brieger, has given the name of pepto-toxine. This substance belongs to the aromatic series, and I shall have again to refer to it when speaking of the action of drugs upon the liver. It causes drowsiness and feebleness, and may possibly be

the cause of these symptoms in some cases of indigestion, but it causes no diarrhoea.

Diarrhoea is, however, one of the most prominent symptoms produced by neurine, choline, and muscarine. Two other alkaloids—mydaleine, and another not yet named—which Brieger isolated from putrefying livers and spleens, have a still more powerful purgative action, producing almost continuous and fatal diarrhoea.

In all probability much of the diarrhoea which occurs, especially in children, after the use of milk, is due to the formation of tyrotoxin, or other more or less poisonous products, by decomposition of the milk in the intestine itself. One of the most fruitful sources of diarrhoea in children is certainly the use of feeding-bottles with long tubes, which are generally imperfectly cleaned, so that even when the milk is put quite fresh into the bottle it becomes inoculated with bacteria before it reaches the child's stomach, where the temperature is just right for their rapid multiplication and the decomposition of the milk. The difference between the chances of a child fed at the breast and in this way is enormous, for in the former case the milk flows free from germs directly into the child's mouth, and the risk of bacterial inoculation is greatly diminished.

Indeed, Andeer finds that in cows there is an antiseptic substance, resorcin, present in the udder, as if for the purpose of rendering the milk not only aseptic but antiseptic.

The possibility of contamination in the child's mouth itself suggests the advisability for careful supervision in regard to the cleanliness of things put into it, even though it only be the mother's fingers or a teething-ring.

There can be, I think, little doubt that choleraic diarrhoea, Asiatic cholera, and typhoid fever are all due to microbes, although bacteriologists may not have definitely settled the nature of the microbe in each case. In choleraic diarrhoea and cholera it is probable that the microbe acts to a great extent indirectly upon the organism by simply producing poisons in the intestine.

Cholera.—As I pointed out, in 1873, the symptoms of cholera are exactly those of muscarine poisoning, and most of the recent researches on the subject have tended to show that these symptoms are due to the action of a chemical poison which may act independently of the microbes which produce it. Lewis and Cunningham showed in 1874 that boiled cholera dejecta would still cause diarrhoea, although any microbe present in them must have been destroyed in boiling. Cantani and Klebs have also obtained symptoms of poisoning from sterilized cultivations of the cholera bacillus. Pouchet obtained an oily base belonging to the pyridine series from cholera stools, and Brieger got from pure cultivations of the comma bacillus in beef broth, in addition to the common ptomaines of putrefaction, two poisons which he regarded as specific products of the comma bacillus. But none of the poisons which have been isolated produce exactly the symptoms of cholera. In Cantani's experiments, tremor, prostration, spasms, and repeated vomiting were observed, while Klebs noticed muscular contractions and alterations of the kidney. The poison obtained by Pouchet irritated the stomach and slowed the heart, while one of Brieger's produced muscular tremor and cramps; the other lethargy, and feebleness of the circulation, with occasional bloody diarrhoea. These facts render it probable that the symptoms in cholera are not caused by a poison formed by the action of the comma bacillus alone, and it is evident that much more extended investigation is required before the pathology of cholera is accurately understood.

In all such investigations, too, one must bear in mind the possibility of the poison being formed not in the intestines merely but in the blood or tissues.

Typhoid Fever.—In typhoid fever the symptoms do not point so much to the formation of a poison affecting the body generally, as to the local action of the microbes upon the intestine, although in some epidemics of typhoid the intestinal symptoms are but slightly marked, while bronchial irritation is very prominent. Whether this bronchial irritation is due to the action of a microbe or to a ptomaine produced by it on the bronchial mucous membrane I cannot say.

TREATMENT OF DISEASES DEPENDING ON MICROBES IN THE INTESTINE.

Coming now to the treatment of diseases depending upon microbes in the intestine, it is evident that the indications are, first, to remove both the microbes and the poisons they have formed as

much as possible; secondly, to neutralise the injurious effects of any poisons already absorbed into the blood; thirdly, to prevent or lessen the growth of any microbes which may still remain in the intestine, and prevent their forming any more poisons.

Eliminative Treatment.—It is curious to watch the changes in medical theory and medical practice, and I remember, when a student, being told that the prompt administration of an emetic would sometimes cause an attack of infective disease to abort. This eliminative treatment has now fallen into disuse, but the present state of our knowledge seems to show that it may not have been without its uses, and it may again be revived. The treatment of diarrhoea by purgatives is still largely followed, and with great advantage. In many cases, if we try to lessen the diarrhoea at once by the administration of chalk or opium, we only make matters worse, whereas a dose of castor-oil with a few drops of laudanum in it, just sufficient to lessen the irritation and not to interfere with the purgative action of the oil, will often put an end to the attack.

It is interesting to notice here, also, how modern researches appear to explain the empirical use of cinnamon water in the chalk mixture with which the dose of castor-oil is so frequently followed up. Cinnamon water no doubt contains a small quantity of tannin, which may have a somewhat astringent action; but the essential oil is probably its most important ingredient. This belongs to the aromatic series, and is probably a good antiseptic; while the oil of cloves, which, along with cinnamon, is an important ingredient of aromatic chalk powder, is an antiseptic of considerable power. Oil from one of the species of cinnamon (*Cinnamomum Cuiilowan*) is regarded in the Molucca Islands as a powerful astringent in cholera.⁶ Another common treatment of diarrhoea is the administration of camphor, which is a powerful antiseptic.

Modifications in Treatment necessitated by the Action of Antiseptics on the Organism.—It is evident that, while we can employ antiseptics outside the body without regard to anything but their power to destroy microbes, yet when we use them for intestinal disinfection, we are obliged to consider the effect that they may produce upon the organism.

When the contents of the stomach are undergoing decomposition either from yeast, sarcinae, or bacteria, we may get good results by the use of creasote or carbolic acid, because these substances come directly into contact with the microbes in the stomach, and a quantity of them which is too small to be injurious to the patient will be sufficient to act as a disinfectant. If the intestine is to be disinfected, these drugs will not produce this effect so readily, because they will be partly absorbed in the stomach, and one has to look either for some remedy which on account of its sparing solubility will pass through the stomach into the intestine without being absorbed, or else one which will not have much poisonous action.

Intestinal Disinfectants.—Several remedies have lately been proposed as intestinal disinfectants. Naphthaline, which has been recommended by Rossbach,⁷ is very sparingly soluble, so much so that it passes to a great extent unchanged through the whole of the intestinal canal. It certainly destroys the disagreeable odour of the motions in infantile diarrhoea, but it does not appear satisfactorily to check the disease. Salol is the phenyl ether of salicylic acid. It passes through the stomach unchanged, but in the duodenum it is split up by the pancreatic juice into salicylic and carbolic acids. Although the carbolic acid is set free at the point where its action is wished, yet there is still the disadvantage of its being poisonous, and so betol has been recommended. The constitution of this substance is similar to that of salol, but it splits up into salicylic acid and beta-naphthol, which is much more sparingly soluble, and which is less poisonous than carbolic acid, while it is much more powerfully antiseptic. Resorcin, thymol, and benzoate of soda are among the antiseptic remedies which sometimes are useful, but these are either weak or subject to the same objections as carbolic acid.

Direction in which to look for Intestinal Disinfectants.—When we consider the enormous number of aromatic compounds which have an antiseptic action, we may expect almost with certainty that amongst them most useful remedies are to be found for diarrhoea, and Pellicani has found that substances containing a diphenyl nucleus are less poisonous, and at the same time more powerfully antiseptic, than those containing a single phenyl nucleus. This

class of bodies is indirectly one in which we ought to search for intestinal antiseptics. But it is quite possible that some of these bodies, otherwise well suited to our purpose, may, like phenol, have an injurious action upon the organism, and the question arises whether this could not be obviated. Phenol and a very large number of the bodies allied to it are excreted in the urine as sulphates, or, to speak more correctly, as ethers of sulphuric acid that is, a sulphuric acid in which one atom of the hydrogen has been replaced by the aromatic radical. Such a combination with sulphuric acid seems to destroy to a great extent the poisonous action of these phenyl compounds upon higher organisms, and by the administration of sulphates the poisonous effect of carbolic acid can be to a great extent neutralised.

Phenyl sulphuric acid, or sulpho-carbolic acid, forms salts with bases, and these salts, though somewhat less powerful disinfectants than carbolic acid, are not nearly so poisonous. They were introduced into medicine in 1869 by Dr. Sansom, and have proved of considerable value as intestinal disinfectants.

As I mentioned before, the diphenyl compounds seem to have less toxic action than those containing a single phenyl group, and possibly the best direction to look for new intestinal disinfectants would be amongst the sulpho-compounds of the diphenyl group.

Sulphonic Compounds: Aseptol.—But there is another class of sulpho compounds, the sulphonic compounds, in which the atom of sulphur, instead of being united by means of oxygen to the aromatic nucleus, is attached directly to one of the carbon atoms in that nucleus. One such compound—ortho-phenol-sulphonic acid, or aseptol, as it has been christened—has been introduced both as a local antiseptic and as an intestinal disinfectant. The commercial aseptol is a solution containing one part in three, and it is administered internally, in the same dose as salicylic acid, in cases both of gastric and intestinal catarrh, and apparently with good results.

STARVING OUT BACTERIA.

Another indication for treatment, besides removing the microbes or destroying their activity, is to starve them out. Although microbes may be able to digest both albuminous and starchy matters—and they may adapt themselves to a certain extent to altered nutrient media so that when accustomed to grow upon albuminous matters they may learn to grow on starch and *vice versa*—yet their action upon the new foods is not so great as that upon those to which they are accustomed.

In Infantile Diarrhoea.—For this reason Vaughan recommends that in infantile diarrhoea the administration of milk should be entirely stopped, as it simply affords nutriment to the bacteria, and is decomposed by them with poisonous substances. In place of it, beef-tea, rice-water, or pure water should be given, and this should be kept up for some days until the milk bacteria have probably died out. Thus we find that the most recent researches bring us back to the practice of Sydenham.

In Typhoid Fever.—The same question comes into consideration in regard to typhoid fever. In the treatment of cases of this disease some years ago, I occasionally allowed farinaceous food rather early, say at the end of the second week, because I thought that if properly softened it could not produce any mechanical irritation upon the intestine, however much ulcerated it might be. But several times the temperature seemed to rise so distinctly after the farinaceous food that I began to be very chary of allowing it, and the only explanation that I could think of was that, somehow or another, it might afford a more favourable nutrient medium to the bacilli.

MICROBES IN SEROUS CAVITIES AND IN WOUNDS.

Other cavities of the body, such as the bladder, uterus, pleura, and peritoneum, may serve, like the intestinal canal, as a place where microbes may grow and form poisons. The same rules as to absorption apply to them as to the intestinal canal, and disinfectants must either be sparingly soluble or not powerfully toxic. This is also the case with wounded surfaces, at least, if the disinfectant is to be kept in constant contact with them, for they absorb rapidly, and, moreover, the antiseptic must have little or no local irritant action. Carbolic acid has the twofold advantage of having a slight local anæsthetic action and being at the same time a powerful antiseptic, but a number of instances of poisoning by its absorption either from wounds or closed cavities into which it has been injected having occurred, surgeons have been for some years looking out for another antiseptic which would possess all its advantages without any of its disadvantages. In this search they

⁶ Husemann, *Arzneimittellehre*, 2te Aufl., p. 570.

⁷ Rossbach, *Berl. klin. Woch.*, 1889, No. 42.

have for a time forsaken carbon compounds, and have resorted to the use of mercurial salts, to some extent at least; but yet, at the same time, a number of new organic substances have been under trial, and have been more or less successful.

Chlorine, bromine, and iodine in their free condition are amongst the most powerful antiseptics we possess, and it seemed likely that the organic compounds containing them in large quantity would have an antiseptic action. Accordingly, iodoform (CHI_3), corresponding in its chemical structure to chloroform (CHCl_3), which is itself antiseptic, but containing iodine in place of chlorine, was tried, and for a while was much praised, but further trials have shown that it is by no means as powerful as an antiseptic, and is perhaps even more dangerous than carbolic acid. Its special advantages were supposed to be that the iodine which it contained was only set free by living protoplasm, and thus it might act as an antiseptic and kill microbes just as sulphur, though itself an inert powder, will destroy the fungus of the vines on which it is sprinkled, because from it the protoplasm of the fungus forms sulphurous acid or sulphuretted hydrogen, by which it is itself destroyed. When sprinkled on a wound iodoform prevents the movements of leucocytes, renders the surface dry, prevents suppuration, and encourages granulation, while at the same time its local anæsthetic action lessens pain. It seems to have a special destructive action on the tubercle bacillus, and is therefore employed with advantage as a local application for tubercular disease of the larynx and tubercular abscesses. One great convenience of iodoform consists in the fact that it can be applied as a powder over any surface, and will there exercise its antiseptic action for a long time without the necessity of any dressing being applied over it, but as I have said, it is not without its dangers, and although sparingly soluble, it may yet be absorbed from wounds or cavities to such an extent as to produce poisoning. The symptoms of poisoning are particularly interesting, as they consist of a peculiar combination of the action of iodine itself with that of an alkyl. Like an iodide, it may produce unpleasant taste and smell, running at the nose, and gastric disturbance, but it behaves also like a member of the alcoholic series in causing special symptoms of poisoning which are connected with the nervous system, and consisting of loss of memory, variable temper, headache, sleeplessness, and especially mental disturbances, sometimes amounting to furious mania, alternating with coma. Fatty degeneration of the heart and other organs is usually found after death.

Iodol.—On account of this poisonous action of iodoform, another organic compound of iodine has been introduced. In this the proportion of iodine is somewhat smaller, and the carbon compound with which it is combined, instead of belonging to the alcoholic or open-chain series, belongs to the class intermediate between it and the aromatic series. In it four carbon atoms along with one of nitrogen form a closed ring, and to this four atoms of iodine are attached. This body, iodol, is a yellowish powder, which can be used exactly like iodoform. It has over iodoform the advantage of being free from any disagreeable odour, and of being less poisonous. In animals, however, it produces in large doses symptoms similar to those of iodoform, and it has the disadvantage of being somewhat more irritant locally.

Soziodol.—As the antiseptics I have already mentioned, although useful, are not without their disadvantages, one would naturally look for something else which might be free from them, and one of the first ideas which would occur to a chemist would be to combine the iodine with some compound of the aromatic series instead of one of the fatty series, as in iodoform, or of the intermediate series, as in iodol. This has been done, and a large number of preparations have been introduced under the name of soziodol. This is a compound of iodine with paraphenol sulphonic acid, which only differs from sozolic acid, or orthophenol sulphonic acid, which I have already mentioned, in the position of the hydroxyl and sulphonic groups. Soziodol forms salts like phenol, the hydrogen in the sulphonic group being replaced by a base. The salts chiefly used have been those of sodium and potassium, and they have been employed either in watery solutions, or mixed with talc or sugar of milk as powders in place of iodoform, or in the form of ointments. Like iodol, they have the advantage over iodoform of being without smell, and, so far as experience has yet gone, they produce no poisonous effect.

Chlorine Compounds.—Another natural idea is to combine chlorine instead of iodine with phenol, and this has been tried. Trichlorophenol contains three atoms of chlorine in place of three

of hydrogen. It has a somewhat disagreeable odour, it is almost insoluble in water, but forms salts, and those of calcium and magnesium have been found to be not only powerful disinfectants, but to have no irritating action on the tissues.

The relation of these antiseptics will be evident from a comparison of their graphic formulæ.

Iodoform.

Iodol.

Soziodolic acid.

Soziodolate of Sodium.

Phenol.

Sozolic acid.
(Aseptol).

Trichlorophenol.

ANTISEPTICS IN LOCAL DISEASES.

The application of germicides is not only useful in cases where the microbes form poisons, which by their absorption may cause general poisoning, but is also of service where the microbes produce only local mischief. Thus, resorcin and iodoform have been of great service in the treatment

of skin diseases, such as lupus, where the disease appears to depend upon, or at least to be constantly associated with, the presence of a bacillus. In such diseases it is easy to apply the remedy freely to the part affected, and also at the same time to remove such parts of the tissue as have been completely infiltrated with the microbes. Even malignant disease has been said to yield to the influence of local antiseptic treatment, and a spindle-cell sarcoma of the tonsil is said to have disappeared under the action of iodoform, although confirmation of such a result is desirable.

TREATMENT OF CONSUMPTION.

The most important result which could be obtained by the local use of antiseptics would certainly be the cure of consumption, and numerous have been the attempts to destroy the tubercle bacillus in the lung by means of antiseptic remedies, either inhaled or conveyed to the lung through the blood. Carbolic acid, salicylic acid, aromatic oils of various sorts, and especially eucalyptus oil, have been employed as sprays or inhalations, and iodoform has both been inhaled and applied by insufflation, especially in cases where the tubercle has affected the larynx. In laryngeal phthisis these insufflations are certainly of use, and even where the disease is confined to the lung a certain amount of amelioration of the symptoms has followed the use of antiseptic measures. It has not been shown that any real cure has been effected by them, and this is not at all wonderful when we consider the difficulty of applying them locally in such a way as to destroy the bacillus without affecting the delicate structures of the lung itself. But the idea seemed feasible that one might be able to introduce into the blood some substance which, during its excretion by the lung, would have an antiseptic action and destroy the microbes without damaging the pulmonary tissues. Accordingly, the treatment of phthisis by enemata, containing sulphuretted hydrogen diluted with carbonic acid, was suggested and largely employed for a short time. It was stated by Claude Bernard that sulphuretted hydrogen is very rapidly eliminated by the lungs; so rapidly, indeed, that hardly any passes into the left side of the heart and the arterial system. Therefore the risk of poisoning by enemata of the gas ought to be very small; yet Orfila had shown many years before that enemata of sulphuretted hydrogen might cause poisoning very rapidly. A case of poisoning by the formation of this gas in the intestines has been recorded by Senator, and experiments by Cash and myself on the absorption of gas from the intestines confirmed Orfila's results. The practice, therefore, seemed not to be without risk, and the occurrence of a fatal case, as well as the smallness of the beneficial results which have been obtained from it, have caused the practice to fall into disuse.

The principle, however, appears to be rather a good one, and the direction in which one would now look is for some substance which would undergo slow decomposition in the intestine or in the body generally, and give rise to volatile antiseptic products which would be slowly but constantly eliminated by the lungs, so that during the whole twenty-four hours the tubercle bacilli would be exposed to its action. Though a volatile substance which would be excreted by the lungs is most likely to be beneficial, yet perhaps it is not absolutely necessary that it should be volatile. A soluble substance circulating in the blood might be efficacious if it possessed a specific power to destroy the tubercle bacillus without injuring the tissues of the lung or acting as a poison to other organs of the body. Such properties are said to be possessed by helenine, which M. Korab found to destroy tubercle bacilli when kept in contact with them. This is a form of camphor which occurs along with alantic oil and alantic acid in the root of elecampane (*inula helenium*). These are all, like other forms of camphor, antiseptics, arresting putrefaction, but having in addition a special power to destroy tubercle. The experiments of Marpmann appear to show that the latter two substances may possibly be useful, as animals to which they were administered did not die when inoculated with tubercle, while others similarly inoculated and which did not receive the medicine died. They have no injurious action upon man, and, after their prolonged administration to phthisical patients, the tubercle bacilli disappeared from the sputum. In cases of phthisis where I have prescribed helenine the patients appeared to improve.

In a most suggestive paper by Dr. Burdon Sanderson he mentioned the destructive effect which phenyl acetic and phenyl propionic acids had been shown by Klein and Lingard to exert upon the bacillus tuberculosis. In consequence of this, Dr. Theodore

Williams tried these substances in cases of phthisis, and apparently with very good results. They may, however, sometimes cause sickness and discomfort in the patient, and are not quite so well borne as helenine. Farther trials are required in order to establish the utility of any of these substances, and to ascertain whether other remedies, having a similar character, may not be discovered and found to be more efficacious.

ACTION OF MICROBES IN THE BLOOD AND TISSUES.

We may now turn from the consideration of microbes and their action when in contact with mucous membranes or raw surfaces to their effect after they have gained an entrance into the circulation. The bacilli of anthrax and of septicæmia in mice probably produce their effect chiefly in the blood, while other poisons, such as those of measles, röteln, scarlet fever, small-pox, acute rheumatism, and tetanus, probably act more upon the tissues. Various theories have been proposed as to the mode in which the anthrax bacillus causes death. One idea was that the bacilli, by aggregating together, blocked the capillaries and caused embolism; a second was that they produced a ferment which decomposed the tissues; a third is that they give rise to one or more definite poisons. It is quite possible that all these theories may be, to a certain extent, correct, and that each of them may represent one factor in the production of the symptoms. The third of them is probably the most important, however, and the symptoms probably depend chiefly upon the formation of a poison. Indeed, Hoffa has obtained from pure cultures of the bacillus anthracis a ptomaine which produces the symptoms of anthrax, and death when subcutaneously injected; but it is not unlikely that the presence of a ferment may aid the anthrax bacillus in the production of a poison. Pasteur showed that the anthrax bacilli did not produce a ferment which was capable of causing the disease when injected, for by filtering the blood of animals suffering from anthrax through porous cylinders, and thus keeping back the bacilli, he obtained a filtrate which was inactive. In all probability, any ferment which the bacilli had formed would have passed through in the filtrate, and would have produced the ordinary symptoms after injection; but Nencki proved this in a way still more free from objection, for he inoculated gelatine jelly with anthrax bacilli. These liquefied the gelatine and fell to the bottom, and the clear liquid which remained above produced no effect on animals. Wooldridge, indeed, claims to have transmitted the toxic power of anthrax to vegetable albumen, organisms being absent.

These experiments appear to prove that if the anthrax bacilli produce a ferment at all, it is incapable of producing the disease. At the same time one must remember that after the injection either of the vegetable ferment, papain, or of sterilized septic blood into animals, Rossbach and Rosenberger found their blood swarming with bacilli. This observation seems to show that the ferment had rendered the blood more suitable for the rapid growth and multiplication of the bacilli.

Puerperal Fever.—In puerperal fever it is probable that the production of ptomaines in the tissues plays an important part, for Bourget isolated several toxic bases from the viscera of a woman who had died of this disease. This would not by itself prove that these poisons had been formed during life, and were not simply the products of putrefaction, but he also obtained from the urine of patients similar bases which were highly toxic, and killed frogs and guinea-pigs when administered by injection. The amount of poison in the urine was greatest when the symptoms were most severe, and diminished when the patients recovered. This fact appears to indicate a connection not only between the poison and the disease but between the gravity of the disease and the amount of poison.

Tetanus.—The pathology of tetanus was for a long time doubtful, and it was frequently ascribed to reflex excitability of the nerve centres due to the irritation of a cicatrix. It is now shown to be in all probability dependent on a bacillus present in earth or other matter contaminating a wound. The difficulty of thoroughly cleansing the infective matter from slight punctures, and the risk of wounds about the hand becoming afterwards infected even when thoroughly cleansed at first, explains why tetanus should so frequently follow very trivial injuries.

When animals are inoculated with matter taken from suppurating points or with the medulla of animals which have died of tetanus, the disease is reproduced, and on microscopic examination a bacillus has been found to be present. From pure cultivations of this bacillus Brieger obtained four poisons. The first,

tetanine, produces tetanus in mice when injected in minute quantity. Another, which he has not named, also causes tetanus, along with a free flow of saliva and tears. Another, tetanotoxine, first produces tremor, then paralysis, and lastly violent convulsions. A fourth, spasmodoxine, causes severe convulsions both clonic and tonic. This discovery of Brieger's renders it probable that the convulsions in tetanus are due to the action of a poison, but we cannot at once assume that this poison necessarily circulates in quantities with the blood, especially as the flesh of animals which have died of the disease may be eaten with impunity.⁸ It is quite possible that it may be formed either entirely or chiefly in the nerve centres, and that only very small quantities of it pass into the general circulation.

Hydrophobia.—In hydrophobia this is very probably the case, and Anrep says that he has isolated a ptomaine from the brain and medulla oblongata of rabbits suffering from a severe form of rabies. This ptomaine is very poisonous, and minute doses cause the earlier symptoms of rabies, while large doses cause the phenomena usually observed in the latter period of the disease. A gradual habituation of the animal to small doses of the ptomaine produced a certain degree of immunity.⁹

Diphtheria.—From cultivations of diphtheria Roux and Yersin have obtained a soluble poison which may cause the symptoms of diphtheria in various degrees of intensity according to the dose. A large dose may cause rapid death, a smaller one may produce paralysis, ending fatally, while a still smaller one may cause only temporary paralysis.¹⁰

This poison, however, is not a ptomaine, that is, it is not of an alkaloidal nature. It appears to be rather acid, ferments, and is destroyed by boiling for ten minutes. The results of experiments already made render it hopeful that it may be possible by its means to confer immunity from the disease, but this is not yet certain.

TREATMENT OF DISEASES DEPENDING UPON INFECTION OF THE BLOOD OR TISSUES BY MICROBES.

There are two lines of treatment which one would naturally pursue. The first is to destroy the microbes or so weaken them that the leucocytes of the blood or the cells of the tissues may be able to complete their destruction. The second is either to eliminate the poisons they have formed, or to use some remedy which will antagonise their action.

The difficulty of destroying microbes by drugs is still greater in the circulation and tissues than it is in the intestinal canal, or in any of the body cavities; for here the comparative solubility of a remedy will not help us. We require one which will destroy the microbes without injuring, or at any rate without injuring to any great extent, the cells of any of the tissues, for it will be carried to them all by the blood. It is quite clear that if the microbes are few in number, so that the fight between them and the leucocytes or tissue cells is a fairly even one, the balance may be turned by the use of a drug which will hurt the microbes more than the organism. Even if it should be somewhat injurious to both, the quantity required to kill the microbes will do the organism no great harm, and the total result will be a cure; but if the microbes are very abundant the antiseptic dose required to destroy them may be so great that it would of itself be poisonous to the diseased animal. We can thus see that experiments with the same remedy may yield very different results in the hands of different observers, and that while some might laud it as a certain cure, others might regard it as of no use whatever. From its general antiseptic power carbolic acid was likely to be the remedy first tried, and Bouley, Davaine, and others employed it in cases of anthrax with a certain amount of success.

Salicylic acid, which is closely connected with carbolic acid in

its composition, differing from it by the introduction of the carbonyl group, has also been tried in a great number of infective

diseases. In most of them it has been of little use, but in acute rheumatism it certainly lessens the pain and reduces the temperature, giving the patient great relief. Whether it cuts short the disease, however, is a question which is not yet finally settled, although possibly the difference in opinion on this subject may be partly due to the different modes in which it is administered. It is evident, however, that amongst the enormous numbers of antiseptic compounds we may yet expect to find many drugs which may be useful as disinfectants in the blood and tissues.

Treatment by Elimination: Purgation: Diuresis.—Another method consists, as I have mentioned, in increased elimination. Free purgation was formerly resorted to, and apparently in many instances with good results, nor is this to be wondered at when we learn that faeces contain large quantities of ptomaines as well as of microbes.

But the most ready channel for the elimination of soluble poisons is the urine, and diuretics have long been used in the treatment of febrile diseases, and are still trusted as amongst the most efficient remedies. Acetate of ammonia with spirits of nitrous ether are still amongst the most favourite remedies as antipyretics.

Washing Poisons out of the System.—One of the best diuretics is a free supply of water, and Ringer pointed out the possibility of lessening the effect of poisons by washing them, as it were, rapidly out of the system.¹¹ This plan has recently been followed by Sanquirico¹² with very striking results. In his experiments he injected quantities of a weak saline solution directly into the veins, immediately after the poison had been administered, or just when the symptoms of poisoning began to appear. By treatment in this way he found that three times the ordinary lethal dose of strychnine had to be administered before death occurred. The poisonous action of chloral, alcohol, urethane, paraldehyde, caffeine, and aconitine was also diminished, but not very much, while that of morphine and nicotine was unaffected. In all cases the beneficial effect of the treatment was most marked when the diuresis was greatest. No doubt the effect of fluids is likely to be greater when they are introduced directly into the veins than when they are introduced indirectly through the alimentary canal, but the effect in both cases will be the same in kind, though different in degree. I think we sometimes follow this plan unwittingly in febrile diseases by feeding the patient on milk, and more especially on milk diluted with soda and potash water. We thus administer a larger quantity of liquid than we should otherwise be likely to do, and the carbonic acid in the effervescing water tends both to aid absorption from the stomach and to stimulate excretion by the kidneys.

Leucomaines.—With the exception of peptotoxine, which is formed by the action of pepsine, I have hitherto spoken of alkaloids which owe their formation to microbes, and which are called ptomaines. But the cells of living organisms also break down albuminous matter in the course of the functional activity, and alkaloids are formed in the healthy body, to which the name of leucomaines has been given. An interesting observation has been made by Bouchard, to the effect that the alkaloids formed during sleep have a stimulating action, so that when they accumulate to a certain extent they tend to excite the nervous system and make the person awake. Those, on the other hand, which are formed during the waking hours have a depressant action, and tend to bring about a condition of sleep. There is thus a sort of self-regulation in the processes of life, by which waking and sleeping are alternately ensured. To this point, however, I shall have to refer again in considering the action of soporifics.

Uræmia.—In health all the poisonous substances formed during tissue-change are excreted chiefly in the urine; but when the kidneys are diseased, or have been in any way rendered functionally inactive, the alkaloids may accumulate and give rise to those symptoms of poisoning which are usually known by the name of uræmia. In cases of disease of the kidney where such a condition has been threatening, an exclusively milk diet proves of the greatest service, and probably does so in a great measure by washing the poison out in the way I have just mentioned, although it is also likely that such a diet tends to limit their production. The objection may be raised that in a good deal of what I have just been saying there is no very obvious relation to chemical constitution. This is quite true, because, though Brieger has pointed out that most of the alkaloids that he has obtained are

⁸ Sormani, *Rendiconti del Reale Istituto Lombardo*, March 28, 1889, quoted in *Nature*, May 2nd, 1889, p. 21.

⁹ Anrep, *Vratch*, No. 2, 1889, p. 52, abstracted in the *JOURNAL*, Feb. 9th, 1889, p. 319.

¹⁰ Roux and Yersin, *Annales de l'Institut Pasteur*, 1888, Nos. 11 and 12.

¹¹ Ringer, *Lancet*, 1883, April 14th, p. 628; Murrell, *ibid.*, April 21st, p. 705.

¹² Sanquirico, *Centralbl. f. d. med. Wiss.*, 1886, p. 929; and *Arch. per le Scienze med.*, vol. xi, p. 275.

either amines or diamines, or else more complicated compounds of nitrogen and carbon allied to uric acid, yet the chemical structure of many of those formed in the body either in health or disease has yet to be discovered. When we know their chemical nature we may be able, in a case of uræmic poisoning, at once to administer an antagonistic remedy and save our patient, instead of standing, as at present, almost helplessly by. A knowledge of the relation of chemical constitution to physiological action is likely to guide us also in our investigations regarding the nature of the poisons in uræmia. One set of poisons is probably allied to uric acid, and may include guanidine, methylguanidine, and other derivatives of urea.

In health the greatest parts of the products of albuminous waste are excreted by man in the form of urea; uric acid occurs only to a small extent. But in various disturbances of nutrition we find that the quantity of uric acid is greatly increased, and that sometimes along with it oxalate of lime makes its appearance. We might, therefore, naturally look for compounds of oxalic acid as among the substances likely to give rise to symptoms of poisoning if retained in the body.

Symptoms of Uræmia.—For my own part, I have sometimes been struck with the extremely rapid pulse in cases of uræmia, although there was no rise of temperature to account for it. This rapidity could hardly occur unless the vagus were either paralysed or inactive, and resembled so much the effect of atropine that I have been inclined sometimes to think that an atropine-like body was giving rise to the symptoms.

Hypothesis as to the Nature of the Poison in Uræmia.—Now there is a substance allied in its chemical constitution to oxalic acid, namely, oxalethylene, which has the power of paralysing the vagus and producing great rapidity of the pulse, just like atropine, which it also resembles in its action upon the pupil and brain, dilating the pupil and exciting the brain. When one atom of hydrogen in this body is replaced by chlorine so as to form chlor-oxal-ethylene, we obtain a body which no longer dilates the pupil, acts upon the brain like morphine, but still paralyses the vagus. We thus have a group of symptoms which closely correspond with those occurring in certain cases of uræmia. Should this substance, or any one nearly allied to it, be found to be present in cases of uræmia, experiments could readily be instituted with a view of finding antagonistic compounds, and the end we desire might be attained. In some cases of uræmia the injection of pilocarpine has arrested the convulsions, and it appears to me more likely to have produced these effects by antagonising the convulsing compound than simply by producing profuse sweating, although such an action might possibly tend to help elimination. This appears to be more likely from the observation of Sânger that pilocarpine is only of use before the occurrence of coma, for this symptom probably indicates either the presence of another alkaloid not antagonised by pilocarpine or an accumulation of poison to an extent which cannot be neutralised.

In Fraser's experiments on antagonism he showed that, while atropine and physostigmine counteracted each other up to a certain point, yet when the dose was too great the presence of both appeared to cause death more quickly even than either the one or the other alone.

PREVENTIVE TREATMENT OF INFECTIVE DISEASES.

In the early part of my lectures I mentioned that just as we can prevent the growth of a crop by destroying the seed or rendering the soil barren, so we may prevent the occurrence of infective diseases, either by destroying the microbes which form the disease germs or by altering the soil, namely, the organism in which they are to grow. We read in history of an ancient custom of rendering the soil of an enemy's city, which had been razed to the ground, barren and waste by sowing it with salt, and in our day we see a similar plan made use of to prevent the growth of grass and weeds on gravel walks. The beneficial results of vaccination for small-pox showed the possibility of sterilising the organism for particular microbes, so that they could no longer thrive in it; and Pasteur's treatment of anthrax with a weakened virus induced men to ask the question—How is insusceptibility to disease induced? and to try whether it was possible to prevent

disease by the administration of chemical substances instead of by inoculation with microbes. One of the most powerful of all disinfectants is corrosive sublimate, and it has the advantage of exerting its antiseptic powers in all kinds of liquids. Koch used it, but without success, as a cure for anthrax, administering it after the disease had already been established. Cash administered it to animals as a preventive, and found that those which had received it for some time before inoculation remained well, while those not so treated died after inoculation. The possibility of preventing infective disease by the administration of remedies was thus proved. Pasteur, with the prophetic insight of true genius, arrived at the conclusion that the active agent in preventing hydrophobia was a chemical substance formed by a microbe and not the microbe itself, and upon this idea his plan of preventing hydrophobia is based. Wooldridge found that when anthrax bacilli were cultivated in beef broth, and the bacilli themselves were removed by filtration, the filtrate containing, as it did, the products which they had formed during their growth rendered an animal into which it was injected proof against anthrax inoculated afterwards. Pasteur and Perdreix found that the blood of animals suffering from anthrax when sterilised and injected into rabbits appeared to protect them against subsequent inoculation. Chantemesse and Vidal have found that the administration of sterilised cultures of the typhoid bacillus protects against subsequent inoculation with the germs, and similar results have been obtained by Roux and Chamberland in regard to septicæmia.

Salmon and Smith have found that a similar treatment with a sterilised culture of the hog bacillus will protect pigeons against inoculation of the said disease, but they have not yet succeeded in protecting pigs. Lastly, also, Pasteur and his assistants have succeeded in cultivating the organism which gives rise to diphtheria. They find that the poison which it produces is most virulent, so that an exceedingly minute quantity of it will produce death. Like the disease itself, this poison will produce paralysis of motor nerves, and it seems probable that the symptoms of the disease are, to a great extent, due to the absorption of the poison from the surface of mucous membrane upon which it is formed. This poison appears not to be of an alkaloidal nature, but rather of an albuminous character, and it is allied to ferments by the fact that it is quickly destroyed by boiling. Inoculation with minute doses of the poison, gradually increased in quantity, will finally not only render an animal insusceptible to the large quantities of the poison, but protect it against the diphtheria when the disease germs themselves are afterwards inoculated.

MODE OF ACTION OF PREVENTIVE INOCULATION.

The tolerance of poison which has been established in the case of diphtheria is probably similar in its character to what occurs during the habitual use of morphine. But perhaps the simplest case of acquired toleration is observed in salmon and other fishes which live at one time in salt, and at another in fresh, water. If such a fish be transferred directly from sea water to river water, or *vice versa*, it would quickly die, the water to which it was unaccustomed at the time acting as a poison to it. But if the transition occur gradually, as it does in the migrations of the fish, where it passes from salt water to brackish, and then to fresh, or *vice versa*, the tissues of its body, especially of its gills, become adapted to the gradual change, and no harm ensues. In the ordinary course of invasion of an organism by microbes, the microbes appear to have the power of secreting some substances which will destroy the cells of the organism. If these are, however, protected against the poison by previous gradual inurement to its action, they resist the microbes and destroy them. The whole subject is still in its infancy, but the results already obtained raise great expectations for the future. There is one point, however, which seems doubtful, and that is the duration of the immunity which may be thus conferred.

Sewill has found that by inoculation with small quantities of snake venom, he can establish a certain tolerance for larger quantities of the poison injected at once; but this tolerance wears off after six months, so that it rather resembles the tolerance which is established for morphine by its continuous use than the immunity against small-pox which is conferred by vaccination. It is possible that the germs of a disease may establish in the cells of the organism which it attacks a power of producing some substance inimical to their growth, and that this power may continue for years unchanged without any external evidence of its presence. Possibly some evidence of such an alteration might be found by careful examination of the poisons excreted in the

urine of an animal before and after preventive inoculation of anthrax, and careful comparison of the action of these substances upon the life of anthrax bacilli. But the whole question is a very wide one, and an enormous amount of patient and laborious investigation will be required before we get any accurate knowledge on the subject.

CHEMICAL STRUCTURE AS AN INDICATION TO THE CHOICE OF ANTISEPTICS.

But there is one inquiry which is of still more immediate practical interest, and that is, which compound is likely to be most powerful as an antiseptic, and least likely to produce at the same time unpleasant or dangerous symptoms. Phenol itself has an antipyretic action, but its poisonous and antipyretic properties run too nearly parallel to allow of its being much used to reduce temperature. On comparing the action of phenol with similar compounds in which two or three atoms are replaced by hydroxyl instead of one, as in phenol, it has been found that the toxic action is, upon the whole, rather increased with the increased number of hydroxyl groups, phenol being hardly so poisonous as resorcin, and this in its turn less poisonous than phloroglucin.

The rapidity of action of these drugs is in inverse ratio to their toxic power; phenol, which is less toxic, acts most quickly, and phloroglucin mostly slowly. Resorcin is apparently intermediate.

But we have not merely to consider the number of hydroxyl groups in the body. We must consider also their position in relation to the benzene nucleus. This nucleus consists of six carbon atoms united together to form a close ring, and to each one an atom of hydrogen is attached, so that we have six hydrogen atoms attached to six carbons, and the formula is C_6H_6 . It is not quite certain how the carbon atoms are united amongst themselves. According to Kekulé, they are alternately united by double and single affinities, while others have proposed connections between atoms on opposite sides of the ring.

We must bear in mind that this ring is simply hypothetical, but it gives us a convenient means both of representing aromatic substances and of studying their relationship.

Whatever the real nature of the connection may be, it appears that the benzene nucleus is symmetrical; and that if we replace an atom of hydrogen in it by hydroxyl, chlorine, methyl, or any other radical, the product is the same whichever atom of hydrogen is replaced. But, if we replace a second atom, the case is different, for the fact that one atom in the original nucleus has been already replaced has rendered the nucleus unsymmetrical. If the second replacement occurs on a carbon atom next to the first, it is represented in a formula by the figures 1:2, and is said to be in the ortho position. If on the next atom but one it is represented in a formula by 1:3, and is said to be in the meta position, and if in the next but two, it is represented as 1:4, and is said to be in the para position. The position of radicals replacing hydrogen in the benzene nucleus affects the chemical behaviour of the compound very considerably.

Thus if an alkyl, such as methyl, be attached to one carbon atom, the attachment of a second negative radical, such as hydroxyl, to the nucleus in the ortho position prevents its oxidation in acid solutions, but hastens it in alkaline ones, and there can be little doubt that the relative position of the radicals attached to the benzene nucleus will affect the processes of oxidation and reduction which it undergoes in the organism, as much as it would do in the hands of a chemist. We have, perhaps, too few data as yet to come to a definite conclusion regarding the exact alterations which the position of a group in the benzene nucleus will effect in its physiological action, but a number of most interesting data have already been obtained. Thus it has been found that in the case of the dioxybenzenes, where two hydroxyls occupy the ortho position, the action is most powerful. It is weakest in the meta position, and is intermediate in the para position in the benzene nucleus.

In the case of the trioxybenzenes where we have three hydroxyls, we find that when these are in position, 1, 2, 3, or are consecutive, as it is termed, the toxic action is greater than when they are in the position 1, 3, 5. In the first instance, as in pyrogallol, any two hydroxyls are to each other in the ortho position, whereas

in the second, phloroglucin, any two are in the meta position to each other. If we replace the hydroxyl in phenol by carboxyl ($COOH$), we lessen its toxic power very considerably, though the substance we obtain—benzoic acid—still has considerable antiseptic power. If we replace one atom of hydrogen in the benzene nucleus by hydroxyl, and a second by carboxyl, we find that the same rule holds good as for the di-oxy compounds. Here, too, the rule regarding position holds good, for salicylic acid, in which the hydroxyl and carboxyl are in the ortho position, is more powerful than either of its congeners meta and para-oxy-benzoic acid, in which they are in the meta and para position respectively.

SUMMARY OF THREE LECTURES ON SOME AFFECTIONS OF THE GENITO- URINARY ORGANS.

Delivered at the Royal College of Surgeons of England.

By MATTHEW BERKELEY HILL, F.R.C.S.,

Senior Surgeon to University College Hospital.

LECTURE I.

DIMENSIONS OF THE NORMAL URETHRA.

BEFORE describing the conditions caused by chronic urethritis, the lecturer briefly enumerated the conditions and variations of the healthy urethra when tested by the meter and examined by the endoscope. The natural condition of the urethra when at rest is that of a tube with its elastic walls closely contracted, capable of yielding to the flow of urine and the passage of a sound much larger than any stream of urine. This expansibility varies in different parts of the canal: being greatest in the prostatic portion. There it reaches to fifty or sixty millimetres in circumference. At the aperture in the triangular ligament it ranges from about forty to about twenty-five millimetres, most commonly it is about thirty millimetres. At the bulb, expansibility of the urethra again is sometimes forty millimetres, when the rest of the penile portion is only thirty millimetres. The meatus varies greatly, twenty-five millimetres being the common size.

When seen through the endoscope, the colour of the mucous membrane is pink, or bluish-pink, varying in different individuals, but identical with the hue of the buccal mucous membrane. The surface has a fine gloss or brilliancy given to it by a thin lubricating layer of mucus. Along the floor two fine furrows course forwards, and towards the deeper part minute carmine tinted papillæ are visible. The openings of ducts can be seen in health in the prostatic portion, but seldom or never in the part anterior to the triangular ligament. The lumen is generally linear when closed, and in the penile part transverse, except at the fossa navicularis, where it is vertical and lozenge-shaped. At the membrano-prostatic portion the lumen is saddle-shaped or arched.

CHRONIC URETHRITIS.

The morbid changes seen in the urethra in chronic urethritis were illustrated by drawings taken by Mr. Frank Collins, and by diagrammatic enlargements of them.

MORBID CHANGES IN URETHRITIS.

Varieties of Urethritis.—Inflammation may invade the tissues in several ways; first, simple mucous catarrh; next, inflammation of the whole substance of the mucous membrane and sub-mucous tissue, and even the erectile tissue; lastly, the glands of Littre and lacunæ of Morgagni are chiefly affected. Near the meatus long ducts open, which occasionally become inflamed, and are very slow to heal. These ducts are most easily seen in persons who have slight hypospadias, as small dots from which muco-pus comes by slight squeezing, and through which a probe can be passed for half an inch. Further down the canal the inflammation may extend along the ducts into the glands of Cowper; and further still, by the ducts into the body of the prostate. Besides these simple catarrhal extensions there are other affections which may be classified as:

1. Superficial granular induration of the mucous membrane.
2. Inflammation of the glands and lacunæ.
3. Areas of deeper induration with proliferation of cells, ultimately converting the mucous tissue into fibrous tissue.