with much better results of operative interference than those which were obtained some years ago. Fourthly, treatment of whatever kind has been subjected to a somewhat unfair and deceptive test, for a large proportion of the cases have been too far advanced when they have presented themselves to be brought to a satisfactory result.

Now, considering the present condition of surgery—that, on the one hand, operative treatment has made great advances, and, on the other, that many observers are more than ever impressed with the reparative power evinced during early life—it is inevitable that, in combating such an affection as tuberculous joint disease, two main but widely diverging lines of treatment should be adopted and worked out, so that they may be weighed the one against the other:—the one being founded on the principle of removing all the affected structures by excision of the joint, so that the remaining structures may undergo sound repair; the other consisting of placing the diseased joint under the most favourable conditions, in the hope that the tuberculous process may undergo arrest, and that recovery may then ensue.

Towards a solution of the question which of these two methods yields the best result, some amount of evidence has already been produced, yet I am afraid a conclusive verdict is still in the distance. For while some surgeons strongly advocate early excision, others do all they can to avoid the operation, and only resort to it when every other available means has been tried and has failed.

It will be remembered that Mr. Barker, my predecessor here, last year, strongly advocated the treatment of tubercular disease of the joints by early and complete excision, and specified the grounds on which his views were based.

All, I am sure, who heard the lectures were impressed with the care and thoroughness with which they had been prepared, and with the earnest and conscientious spirit in which the subject was treated. The case for excision, in fact, was presented in a manner which rendered full justice to it, and nothing was left unsaid that could be wisely urged in its favour.

It thus becomes necessary, unless judgment is to go by default, that the case, if there is one, on the other side should be presented, and that it should be shown what objections there are to early excision, and what results can be obtained by an alternative method of treatment adopted at a similar stage of the disease. I will discuss these inquiries in the next lecture.

THE CROONIAN LECTURES

ON THE RELATIONSHIP BETWEEN

CHEMICAL STRUCTURE

AND

PHYSIOLOGICAL ACTION.

Delivered before the Royal College of Physicians of London.

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LECTURE IV—(Continued).

CIRCULATION.

THE state of a patient's circulation has always been regarded as the most important guide the physician can have in regard both to prognosis and treatment. The arms of our college exhibit a hand feeling the pulse as the most characteristic act of a physician.

Test for Life.—As the old adage has it, "While there is life there is hope," and life can never be regarded as extinct while circulation continues. One of the best, if not the best, tests whether life is actually extinct or not is to tie a piece of thread with moderate tightness round the finger. If the person be quite dead no change will occur, but if there be any circulation, however slight, the end of the finger will gradually swell. Even after death has occurred and circulation has ceased in the body generally we are able to maintain the functional activity of isolated organs by means of artificial circulation, so that the lung retains its vitality, the muscles their conductivity, and the glands their secreting power for hours or even for days after the rest of the

body to which they belonged are dead. On the other hand, if the circulation in an organ be arrested by contraction, plugging, or pressure upon the vessels supplying it, its function is quickly abolished, although the other parts of the body may be perfectly healthy.

"Faint Heart never won Fair Lady."—Feeble circulation leads to poor nutrition and general weakness and inefficiency, so that a faint heart has become proverbially unsuccessful. A stout or strong heart, on the other hand, leads to active circulation, good nutrition, general power, and success in life. By keeping up an abundant supply of blood to the tissues, it removes the acid products of waste which, as we have seen, powerfully tend to interfere with oxidation. But possibly this is not the only effect of a powerful heart.

Chemical Uses of the Pulse.—According to Fleischl, the shock of the blood sent into the capillaries at each cardiac systole has a mechanical action in aiding the chemical processes of tissue change, in somewhat the same way, though to a less extent, as a blow upon a percussion cap. It is therefore of the utmost importance in the treatment of disease to maintain the action of the heart, and to stimulate it when it is flagging.

Beef-tea as a Cardiac Stimulant.—It is curious to note how a well-grounded practice often holds its own amid changes of theory, and beef-tea still maintains a foremost position amongst our cardiac stimulants. We have other drugs which increase the power of the heart, and which are most useful in their place: digitalis, strophanthus, convallaria, adonis vernalis, and erythrophœum, and the whole class of drugs usually known as cardiac poisons. Unfortunately these drugs do not always give us the result we desire, and at present we are often unable to say why they fail. We do not know their chemical constitution, and therefore we cannot modify it or produce at will drugs having a similar but not identical action, as we can, to a certain extent, in the case of antipyretics and analgesics. Starting from beef-tea, however, we may perhaps obtain what we want. One of the constituents of beef-tea is xanthine. This has a very powerful action on voluntary muscular fibre, but its effect on the heart requires to be more carefully made out.

Caffeine as a Cardiac Tonic.—Methyl xanthine, or caffeine, is now recognised as an important cardiac tonic. Like xanthine, it tends to increase the contraction of muscular fibre, both voluntary and involuntary, and, when its action is pushed far enough, it produces an extraordinary state of muscular rigor. In consequence of this, voluntary muscles dipped into a solution of it frequently contract to the utmost extent of which they are capable, and when applied to the frog's heart it causes the beats to become slower and the heart more and more contracted, until it ceases to beat in systole. In this action it agrees with the other cardiac tonics, like digitalis; but a curious point is here to be noted.

Paradoxical Action of Caffeine.—Although it usually causes firm contraction of the frog's muscle, yet sometimes it causes none at all, and Cash and I have actually found it cause elongation. At present we are unable to explain this curious phenomenon with certainty.

Possible Transverse Contraction and Active Elongation of Muscle.—To me it seems most readily explained on the supposition that muscular fibre, both voluntary and involuntary, not only contracts longitudinally and thus becomes shorter, but may contract transversely and thus become longer. The varying conditions, which Cash and I have observed in the frog's muscle under the influence of caffeine, may be explained by supposing that usually the longitudinal contraction is greater than the transverse, and therefore the muscle shortens; that occasionally the longitudinal and transverse contraction occur together and counteract each other, so that the muscle retains its usual length; and finally, that occasionally, though rarely, the transverse is greater than the longitudinal contraction, and therefore the muscle becomes elongated.

Practical Bearing of Physiological Questions.—But some men may say, What does it matter to us whether a frog's muscle, dipped in caffeine, becomes longer or shorter, and what possible connection with medicine can a discussion have on the question whether its fibres contract transversely as well as longitudinally? And yet it is a matter of vital importance to a patient with mitral disease whether the muscular fibres of his heart will shorten sufficiently to expel the blood from his ventricles or whether they will remain quiescent altogether, or actually elongate, so that the heart stands still in full diastole.

Necessity of Investigation of the Action of Simple Drugs on Simple Tissues.—It is only by a thorough knowledge of the conditions which cause bodies of simple chemical structure like caffeine or xanthine sometimes to produce contraction and sometimes elongation of muscle that we can hope to treat cardiac disease with certainty, either by means of these substances or by more complex cardiac tonics. The only indication that we have of life is motion, either of the body as a whole or its parts, as in the movements of the respiration or pulse, or of the blood in the test for life I have already mentioned, or in secretion, as in the case of glands kept alive by artificial circulation. In order to understand thoroughly the effect of any drug we must know what its action is upon muscular fibre, and the variations produced in its action by changes in the temperature or reaction. But muscular fibres are usually stimulated to contraction or to relaxation by efferent nerves, and they are again excited by the nerve centres from which they proceed. Unless we know the action of drugs on nerves, as well as on muscles, we cannot rightly estimate their action upon nerve centres. It is on this account that Cash and I have not only taken up the study of comparatively simple drugs, such as ammonia, compound ammonias, alkalis, earths, and the simpler aromatic compounds; but we have worked more especially at the action of those substances on muscle and motor nerves, hoping in this way to lay a foundation for future researches on higher structures and more complex drugs.

Modifications in the Action of Drugs.—The action of drugs upon voluntary muscle is not always alike. It may be different in frogs and mammals, nay, more, it may differ in two species of frogs. It may be different in voluntary and involuntary muscle, and the involuntary muscular fibre of the heart may not react in quite the same way as that of the vessels, and the intestines may differ from both. Yet a general likeness can usually be discerned between the action of a drug on all kinds of muscular fibre, and it is precisely the fact that differences exist which will give us most assistance in treatment, after we have once learned the causes of these differences. Caffeine usually, as I have said, contracts the muscles of the frog's legs, but sometimes it elongates them, and the same difference in its action is observed in the heart. Generally the heart stops in systole, but sometimes it stops in full diastole. In this respect the action of caffeine resembles that of digitalis.¹¹

Complexity of the Heart.—In the heart we are not dealing with muscular fibre only, but with nerves and ganglia as well, and the effect of any drug upon this organ is the resultant of its action, not only upon all these structures in the heart, but upon the medulla as well. Moreover, when we are dealing with the heart in connection with the blood vessels the action becomes still more complex, for contraction or relaxation of the vessels will alter the resistance which the heart has to overcome. The problems we have to solve in looking for new cardiac tonics are, therefore, far from easy, but we may hope that patient investigation will solve them, and that we may ere long aid the sufferers from cardiac disease more efficiently than we can at present.

Direction in which to Look for Cardiac Tonics.—I have already pointed out that most drugs belonging to the class of cardiac tonics are also local anaesthetics, but all local anaesthetics do not appear to be cardiac tonics. Nevertheless, by looking through the class of local anaesthetics we may perhaps find some new cardiac tonics, and, at any rate, it is worth while to try.

ACTION OF DRUGS ON THE BLOOD VESSELS.

Our knowledge of the chemical nature of drugs which dilate the blood vessels is somewhat greater than of those that contract them, for the agents which cause dilatation most markedly are of very simple chemical structure. They are, in fact, nitrites, or substances which yield nitrous acid in the blood, but all nitrites have not an equally powerful action, and the efficiency of the NO₂ depends to a great extent on the radical with which it is combined, and the mode in which this combination occurs. For

the group NO₂ may be arranged thus: $\begin{array}{c} \text{O} \\ \diagup \\ \text{—O—N=O, or —N} \\ \diagdown \\ \text{O} \end{array}$

In each of these the nitrogen is trivalent. But it may be quin-

quevalent, in which case the group would be $\begin{array}{c} \text{O} \\ \parallel \\ \text{—N} \\ \parallel \\ \text{O} \end{array}$. In nitrous

compounds, it is probably O=N—O—, while in nitric compounds

it is probably $\begin{array}{c} \text{O} \\ \parallel \\ \text{—N} \\ \parallel \\ \text{O} \end{array}$. But in nitrous compounds we have two

classes: nitroso and iso-nitroso. We thus see that there may be considerable differences in the NO₂ groups, and the action of this group is determined to a considerable extent by the alkyl to which it is joined and the manner in which the joining takes place.

Nitrites of Methyl, etc.—When we have the junction taking place through oxygen, the group NO replacing hydrogen in alcohol, we obtain the nitrites of methyl, ethyl, propyl, butyl, amyl, and so on, but when we have the nitrogen directly united to carbon by one affinity, the group NO₂ replacing hydrogen in methane, we get the nitro compounds, nitro-methane, nitro-ethane, nitro-propane, nitro-butane, nitro-pentane.

Action of Nitro-methane, etc.—These nitro compounds appear to have less action on the vessels than the nitrites, and do not cause the same marked dilatation in them or consequent fall of blood pressure. They tend rather to produce narcosis, like the haloid compounds, chloroform, etc.

Amyl Nitrite.—Amyl nitrite has a rapid action, quickly occurring and quickly passing off, and since I first used it for angina pectoris in 1867 its utility in the treatment of this disease has become almost universally recognised.

Other Nitrites.—While working in Ludwig's laboratory in 1869 on the action of this drug, I satisfied myself that other nitrites, and especially that sodium nitrite, had a similar action. In 1876, Dr. Gresswell and I made some experiments, which we have not published, although a preliminary note appeared of them at the time. From these experiments it appeared that amyl nitrite had a more marked action than ethyl nitrite, but the next in the series, capryl nitrite, was less active than amyl. Recently the subject has again been taken up, and Cash and Dunstan have found that butyl nitrite is still more powerful than amyl, but the question now arises, which butyl or amyl is it whose combination with NO₂ is most efficacious, that is to say, which acts most quickly and most powerfully.

Tertiary Amyl Nitrite.—According to Bertonì the nitrite obtained from tertiary amyl alcohol or ethyl-dimethyl-carbinol acts more powerfully and for a longer time than ordinary amyl nitrite. My assistants have tested it for me, and laboratory experiments showed that in animals, while it caused fall of blood pressure, it also produced vomiting. In one middle-aged patient suffering from angina pectoris it was not so efficacious as ordinary nitrite, and in him it produced vomiting; but in an old man it produced no vomiting, and gave more relief than other nitrites. It is possible that there may be a difference in the effect of the different nitrites in consequence of greater or less rigidity of the vascular walls. It is possible that where the vessels are not rigid ordinary amyl nitrite or iso-butyl nitrite may be best, but when the vessels are rigid a more prolonged action may be desirable, and in these nitro-glycerine and Bertonì's nitrite may be preferable.

Bright's Disease.—But there are other cases in which prolonged dilatation of the vessels is very desirable. First, in cases where the heart is weak and barely able to carry on the circulation; secondly, where the tension from the vessels is very high, and there is danger of rupture, as in cases of Bright's disease. In both of these it is highly probable that we may obtain better results with the nitrites of some of the higher alkyls than with any that have yet been employed. A series of experiments is also desirable on the action of nitro-butane, nitro-pentane, and other nitro compounds in these cases.

ACTION OF DRUGS UPON THE BLOOD.

In addition to the power to dilate the vessels, nitrites have a

¹¹ Cf. Lauder Brunton, *On Digitalis*, pp. 96, 104. London. Churchill, 1868.

very marked action upon the blood. When mixed with it they cause it to become of a chocolate colour, and they produce a similar change in it while it is still contained in the vessels of animals poisoned by nitrites. As Gamgee showed, nitrites, as it were, lock up oxygen in the hæmoglobin, so that blood which has been acted upon by them will not either take up or give off oxygen so readily as normal blood, but strong reducing agents will remove the oxygen, and then the reduced blood will combine with oxygen readily again. On this account nitrites do not arrest the respiration in the tissues in the same way as carbonic oxide, for when they have brought the animal to the verge of suffocation by locking up the oxygen in oxyhæmoglobin, the nitrous compound becomes reduced, and the hæmoglobin then resumes its normal functions. A few inhalations of the nitrites, such as amyl nitrite, may thus produce asphyxial convulsions, but the animal recovers quickly and certainly unless the inhalation be maintained. The nitrite appears to behave to the oxygen of the blood corpuscles in somewhat the same way as the stopper of a bottle does to the liquid it contains, preventing anything from going out or into the bottle, but when sufficient force is applied to withdraw it, it no longer interferes with either exit or entrance. A similar effect is produced by nitro-glycerine and also by hydroxylamine. Nitrites must almost necessarily interfere with oxidation of the blood, and probably it is on this account that they give rise to the appearance of sugar in the urine. Nitrites, notwithstanding their marked effect upon hæmoglobin, do not destroy blood corpuscles, and consequently do not give rise to the presence of hæmoglobin in the urine; but a number of substances, more especially those belonging to the aromatic group, like toluylene-diamine, have this power, and an interesting question arises how far paroxysmal hæmoglobinuria may not really be a form of poisoning, due to the absorption of poisonous compounds of the aromatic series, and pernicious anæmia has been attributed by Sandoz¹² to poisoning by substances formed in the intestine and absorbed from it.

ACTION OF DRUGS ON THE LIVER.

For a long time the liver, notwithstanding its great size and its remarkable position, was regarded as having little functional importance, and was supposed merely to excrete bile, a fluid which plays quite a minor part in the digestive processes. But for some years back the liver has been gradually increasing in importance, and its functions are now recognised to be various in kind as well as most necessary to the organism.

Bile only a By-Product although a Useful One.—The coal tar refuse of gas works is now utilised, at least in large towns, but even in small places gas continues to be made, although the coal tar produced in the process cannot be worked up, and remains simply as refuse. In the same way the bile is certainly useful in the digestive process, preventing decomposition, accelerating peristalsis, and aiding the pancreatic juice to digest fats. But still it is, after all, to be regarded as a by-product of hepatic activity.

Dangers to Life.—The knowledge which we have gained during the last few years regarding the poisonous properties of some albuminous substances, and of the products which albumen yields when decomposed, makes it, as Mr. Darwin said, a wonder that we are all alive considering how many poisonous substances are constantly formed in the intestine.

The Liver as a "Gatekeeper."—Indeed, one can hardly see how life would continue long were it not that the liver has a position and function like the gatekeeper or porter of a town or castle in times of war, inspecting all comers and turning back those that are dangerous. It possesses a twofold power to prevent poisons entering the portal vein from passing into the general circulation, for it turns back some and destroys others. Some of them, such as lead, copper, mercury, and iron are simply arrested by it, and instead of passing into the general circulation are excreted by the bile, and finally ejected from the body. Some organic poisons, such as curara, appear also to be partly excreted in the same way. But the liver appears to have not only the power of excreting poisons but of actually destroying them, or, at any rate, converting them into non-poisonous compounds. Thus double the quantity of strychnine, veratrine, quinine, and morphine are required to kill an animal, if injected into the portal vein, as would be sufficient if injected into the jugular vein, while no less than three times the quantity of curara is requisite.¹³ The liver exerts a similar power over peptones and ptomaines, as well as

over compounds of ammonia with weak acids, such as ammonium acetate, but chloride of ammonium is unaffected.

Uses of Glycogen in Regard to Poisons.—Organic poisons appear to have their activity lessened in the liver by combination with glycogen, for when animals are made to fast, the power of the liver to destroy the toxic action of poisons gradually diminishes as the glycogen disappears. In cases where ptomaines are found in quantity in the intestine, Roger recommends such food to be given as will quickly supply glycogen, such as milk. He explains the usefulness of milk in uræmic poisoning in this way, while beef-tea in such cases simply increases the poison. It is possible that the peculiar symptoms of tremor, faintness, and even mental weakness which occur in some patients when fasting, and which are rapidly relieved by food, may be, in some degree, due to the ptomaines formed in the intestine, and the relief by food may be explained by their destruction by the increased activity of the liver. At the same time we must remember that ptomaines—or, perhaps, we ought rather to say leucomaines—are formed in the tissues generally, and that an increase of glycogen in the blood may combine with poisonous products in the nerves and muscles, preventing them from exerting a poisonous action, and thus removing weakness, languor, or tremor due to them. The whole of this subject presents a fruitful field for further inquiry, and at present our knowledge is little more than sufficient to indicate how much there yet remains to be known.

GLYCOGENIC FUNCTION OF THE LIVER.

Another most important function of the liver is that of forming glycogen. It does this both from proteids and from carbohydrates, and thus acts, one might say, as the coal bunker of the body, storing up a reserve of nutriment to be utilised during the hours of fasting. But here again, we meet with a curious action of some drugs.

Action of Ammonia.—Ammonia, as I have mentioned, is a poison, and so is ammonium carbonate if injected into the jugular vein, but the poisonous activity of these substances is greatly diminished when they are injected into the portal vein. But this is not all. The liver actually converts these poisons into food, and when they are given to an animal, along with a non-nitrogenous diet, they increase the quantity of glycogen in the liver, and ultimately pass out in the form of urea, just as albumen would have done. Some amido-compounds, such as asparagine, and glycocholl, have a similar action, but this is not shared by all the amido substances, for beef-tea, and Liebig's extract, contain a number of these, and yet neither seems to act in the same way as ammonia.¹⁴

Removal of Glycogen from the Liver.—Notwithstanding all the labour that has been expended in investigating the glycogenic function of the liver, it cannot be said that we clearly understand, even yet, the way in which glycogen is formed in the liver, or the way in which it disappears from it. Probably, a good deal of it is carried off by the blood in the form of sugar, and some also in the form of glycogen.

Action of Poisons upon Glycogen.—We have already seen that glycogen unites with some poisons, such as morphine, and with peptones, or other poisonous products of albuminous decomposition, so as to alter their properties and lessen their poisonous activity. We might therefore expect the converse to be the case, and look for them to exert an action upon glycogen, and perhaps render it less easily decomposed. We can readily understand on this supposition how the addition of a single egg, or piece of cheese, to a meal of bread and butter will increase its staying power, so that a person will be able, with this slight addition, to go on for four or five hours, instead of wanting another meal at the end of two. It would also explain the action of morphine in cases of diabetes. As Claude Bernard found that reflex dilatation of the hepatic artery would increase the transformation of sugar in the liver and induce diabetes, one was inclined to attribute the beneficial action of morphine or codeine to their sedative action on the nerve centres, preventing any irritation which might exist from affecting the hepatic vessels. But Mitchell Bruce has clearly shown that this is not the case, and that we must look to a direct action of morphine upon the liver itself for an explanation of its utility in diabetes.

Glycosuria caused by Drugs.—There are a number of substances which will produce temporary glycosuria. Many of these are supposed to act by dilating the hepatic artery; for example, amyl nitrite, curara, ortho-nitro-propionic acid, and methyl delphinine,

¹² Sandoz, *Corr. Bl. f. Schweiz. Aerzte*, 1887.

¹³ Roger, *Action du Foie sur les Poisons*.

¹⁴ Paul Bahlmann, *Inaug. Diss.*, Erlangen, 1885.

chloroform, chloral hydrate, alcohol, and hydrocyanic acid. It is not improbable, however, that some of these at least, may cause sugar to appear, by lessening the normal processes of oxidation, by which it ought to be converted into carbonic acid. For carbonic oxide is a most powerful agent in producing glycosuria, and amyl nitrite, alcohol, and chloroform all tend to lessen oxidation. The most remarkable substance in producing glycosuria seems however to be phlorizin.¹⁵ This substance, which is obtained from the root bark of apple trees, appears to have the power of preventing the organism from oxidising or otherwise utilising sugar. When dogs are kept without food for several days, but receive phlorizin all the time, the whole of the glycogen disappears both from the liver and the muscles; but if they are still kept without food, quantities of sugar appear in the urine, which can only be produced, so far as one can see, from the breaking up of the albuminous tissues of the body. In birds phlorizin causes glycosuria even after the liver has been extirpated.¹⁶ Arsenic, antimony and phosphorus all cause the glycogen to disappear from the liver,¹⁷ but they produce at the same time fatty degeneration, whereas phlorizin appears simply to cause a general shrinking of the liver.¹⁸

Amount of Bile as an Index to Functional Activity in the Liver.—The secretion of bile, although it has attracted more attention than the other functions of the liver, is in itself of minor importance. But just as a stranger visiting a gas-factory in the country, where they could not use up their waste products, might judge by the amount of tar he saw about whether they had been making much gas or not, so from the secretion of bile we may draw important conclusions regarding another very important function of the liver, namely, its power to destroy blood corpuscles. Life appears to consist of a continual process of destruction and repair, and the blood forms no exception to the rule. Its vitality appears to be maintained by constant formation and destruction of blood corpuscles. Whether the corpuscles be actually broken up in the spleen, and their fragments carried to the liver, or whether they be destroyed in the liver itself does not at present concern us.

Relation between Blood-pigment and Bile-pigment.—At all events it is in the liver, or rather perhaps we should say in the bile, that we find the remains of one of their most important constituents, hæmoglobin. Since Virchow pointed out the relationship between hæmatoidin and bile pigment, numerous researches have been made, to show that hæmoglobin could be converted into bilirubin.

Hæmoglobinuria and Jaundice.—Thus, Kühne found that bile pigments appeared in the urine after the injection of hæmoglobin into the blood, and the same result has been observed after intravenous injection of substances which will dissolve corpuscles in the vessels such as bile acids, large quantities of water, ether, chloroform, and phosphoric acid. In trying to repeat some of these experiments, many years ago, I obtained a negative result, and other observers have also failed. In place of bile pigment I found hæmoglobin, and others have done the same, but Stædeleman has cleared up the discrepancies. In his researches on toluylene-diamine, he found that in some animals he obtained hæmoglobinuria, and in others jaundice. This jaundice was due to the fact that the bile ducts became plugged by bile so thick that it would not flow along an ordinary test tube, and much less through the hepatic ducts. The mode of action of the poison with which he experimented, as well as of chloroform, water, or bile acids injected into the circulation, seems to be as follows: They break up the blood-corpuscles, liberating hæmoglobin. This is carried by the blood to the kidneys and liver as well as to the other organs. In the kidneys it is partly excreted, giving rise to hæmoglobinuria. In the liver it is taken up by the hepatic cells and converted into bile pigment.

Hæmatogenous Jaundice.—At first the whole quantity of bile is increased, solids as well as liquids, so that toluylene-diamine may be looked upon as a most powerful hepatic stimulant. Soon, however, the solids increase out of proportion to the fluid in the bile. It becomes thicker and thicker, until it will no longer flow along the ducts, and then a part of it being absorbed from the biliary capillaries, jaundice is produced. These researches show that although all jaundice may be looked upon as of hepatic

origin, yet the function of the liver is so much affected by the nature of the blood, that jaundice may occur in consequence of the destruction of red blood corpuscles, and the name of "hæmatogenous" as applied to such a form of jaundice, may therefore be justified.

Jaundice from Poisons.—One of the oldest observations on jaundice of this sort is probably that of Galen, that the skin becomes yellow in some persons after the bite of a viper. This is particularly interesting in relation to the possible causation of epidemic jaundice, or even of so-called catarrhal jaundice, in those cases where the catarrh is supposed to affect the bile ducts only, and there is no evidence of its extension to the intestine or stomach. The venom of poisonous snakes, both viperine and colubrine, paralyses both motor nerves and nerve centres, but the viperine poison differs from the colubrine in its effect upon the blood, which it deprives of its coagulating power, while at the same time it tends to destroy the red corpuscles. The researches of Weir Mitchell, Reichart, Martin, and Wolfenden have shown that the poisonous substance in snake poison is not an acid or an alkaloid, but an albumose similar in its chemical reactions to the products of the ordinary digestion of albuminous foods in the stomach or intestine. It is only within the last few years that the poisonous properties of albumoses have been recognised, but poisons belonging to this class are now found to be pretty widely distributed.

Poisonous Blood in Fishes.—They occur, according to Martin, in the jequirity or abrus seed, and Mosso has recently found the blood of lampreys and hag fishes, and Springfield that of eels, to be poisonous from albumoses which it contains. The poisonous properties of albumoses are destroyed by boiling, and usually also by the simple process of digestion; but if they should be taken in large quantity into the stomach they might be able to pass through the liver in sufficient quantity to prove injurious, and, if this be so, one can thus understand why Henry I. of England should have died after eating lampreys to excess.

Epidemic and Catarrhal Jaundice.—At present we are quite ignorant of the pathology of epidemic jaundice, or of those cases of catarrhal jaundice where yellowness is the only symptom, and it seems not improbable that both of these may be due to poisons of some sort absorbed from the intestine. I know of one case at least in which jaundice of this sort came on after eating ham which appeared to be tainted.

Acute Red Atrophy of the Liver.—In another case, which I saw only a few months ago, sudden illness came on a few hours after eating ham. I diagnosed the case as one of poisoning by ptomaines. Death occurred in a few days, and the *post-mortem* examination showed nothing to account for death, excepting the liver, which was in a condition of red atrophy. This also is a disease of whose pathology we are ignorant, and further researches must decide whether or not it may really be simply due to the effect of poisons on the organ.

NEW REMEDIES IN DISORDERS OF THE LIVER.

But an extended knowledge of pathology is not the only gain we may hope for from a thorough investigation of the action of drugs upon the liver; we may reasonably expect great additions to our power of treating its functional disorders or even organic diseases. I have already mentioned the peculiar effect of ammonium salts upon the glycogenic function. Dr. Stewart's introduction of chloride of ammonium in hepatic abscess is a most important aid in the treatment of that disease. The biliary function appears to be modified in a remarkable way by many substances of the aromatic series which greatly increase the bile. It is a very remarkable thing that a great number of ptomaines belong to the class of compound ammonias or amines, and the remarkable action of toluylene-diamine appeared to me to indicate the necessity for ascertaining if possible what effect would be produced on the liver by bodies of the aromatic series, free from nitrogen, as compared with the effect of similar bodies combined with ammonia. At my suggestion Dr. Collins made a number of experiments with toluene and toluylene-diamine in my laboratory, and found that both these substances greatly increased the flow of bile. Not feeling quite certain what effect toluylene-diamine and allied bodies might have upon patients, I felt a little chary of using them until I should obtain fuller knowledge of their mode of action. In order to be ready, however, to use them as soon as I had acquired sufficient knowledge, I asked Messrs. Burroughs and Wellcome to prepare me some tabloids and capsules containing toluene and toluylene-diamine. This they kindly did, and a gen-

¹⁵ Von Mering, *Verh. d. h. Congress. für inn. Med.*, 1887.

¹⁶ Minkowski and Thiel, *Arch. f. exp. Path. u. Pharm.*, Bd. 23, p. 142.

¹⁷ Salkowsky, *Virchow's Arch.* 34, p. 78.

¹⁸ Ueber d. Einfluss v. Giften a. d. Grösse d. Leberzellen, A. Neumann, *Inaug. Diss.* Berlin, 1888.

tleman to whom Dr. Collins had mentioned the existence and probable use of the tabloids tried them upon his patients with good success, as he informs me.

Vegetable Cholagogues.—Most of the vegetable hepatic stimulants, iridin, euonymin, and aloes, belong to the aromatic series, although we do not know their chemical structure. Much benefit is frequently obtained by their use in so-called "biliousness," and we may reasonably expect that a full knowledge of the mode of action and chemical structure of the vegetable cholagogues will enable us, not only to apply them more judiciously, but to modify their structure, and consequently their action in various directions, to suit our wants. It is almost certain, also, that we shall obtain a very large series of new bodies which may act upon the liver, either as stimulants or as depressants, increasing or diminishing the formation of bile, and affecting the other functions of the organ, which I have already mentioned. The frequency with which functional hepatic disorder occurs, and the great discomfort which it occasions, not only to the sufferer, but to his friends, and even to the community at large, renders it most desirable that efficient modes of treatment should be discovered.

METHODS OF SEARCHING FOR NEW HEPATIC REMEDIES.

The search after new remedies has hitherto been conducted almost entirely in two ways: first, by the administration of drugs to patients, and a chemical analysis of the liver itself so as to ascertain whether the amount of glycogen and fat has been altered by the drug. According to Ellenberger and Baum, who experimented on horses, the hepatic cell when in action is larger, has a sharper contour, has a net-like arrangement of its proto-

phenone, azobenzine, dibromazobenzene, dimethylparaphenylenediamine sulphate, martius yellow, orthonitrophenyl propionic

Fig. 1.—Fasting liver. Rabbit 6 weeks old. Last food, 18½ hours before death.

plasm, and contains more granules which stain with eosin, and fewer pigment granules than the cell when at rest. This active condition of the cell occurs during digestion, but it may be produced independently of digestion by such drugs as pilocarpin, muscarin, and aloes. A similar but less powerful action is exerted by salicylate and benzoate of soda and by rhubarb. On the other hand, atropine arrests the activity of the liver, so that the hepatic cells appear to be completely at rest, even in the very middle of the digestive process. A similar but less powerful action is exerted by ammonium chloride, sulphate of magnesia, and calomel. Copper and lead also arrest the hepatic activity, but when they are given for a time they produce fatty degeneration of the cells and accumulation of bile in them. The action of a very large number of substances on the liver cells has been investigated by Alfred Neumann under Ehrlich's direction; and many belonging to the aromatic series have been found to produce enlargement of the hepatic cells. Amongst these are cocaine, coumarin, aceto-

Fig. 2.—Active liver. Rabbit 6 weeks old. Killed 6 hours after meal.

acid, paraoxybenzaldehyde, paratoluidin, phenanthroquinone, and phenylthiourea.

Dr. Sheridan Delépine has kindly examined for me the changes which the hepatic cells in the rabbit undergo under the action of atropine, pilocarpine, and toluene. It will be seen from the

Fig. 3.—Action of atropine on an active liver. Rabbit 6 weeks old. Last food, 5.30 hours before death. Injection of 1/160th gr. atropine 3.25 hours before death.

accompanying figures that the effect of atropine and pilocarpine on the liver of the rabbit resembles that which Ellenberger and Baum have described as occurring in the horse.

The effect of toluene is very peculiar. The outline of the cells becomes sharp, but the cells become small and the blood vessels large, so that the liver is congested. The bile also appears to be

expelled from the liver, for the blood corpuscles in the vessels are not destroyed, while they usually are dissolved by the bile.

This subject is one of the greatest possible practical interest, because its investigation may explain the causation of those very common and very troublesome symptoms to which the term

Fig. 4.—Action of pilocarpin on a fasting liver. Rabbit 6 weeks old. Last food, 17½ hours before death. Injection of ½ gr. pilocarpin 1½ hour before death.

“biliousness” is commonly given, and which are usually ascribed to a “torpid liver.” Experiments on the effects of nitrogenous and non-nitrogenous foods on the liver cells are required in order to give us a firm physiological basis; and then a study of the

Fig. 5.—Action of toluene on fasting liver. Rabbit 6 weeks old. Last food, 20 hours before death. Toluene, 1 minim, 4½ hours before death.

action of various substances belonging to the aromatic and ammoniacal groups may enable us to discover what products of albuminous decomposition in the intestine lead to hepatic congestion, “torpid liver,” and “biliousness.” At the same time, we may

hope that such an investigation will also enable us to find efficient remedies for these conditions. At all events, I think it is evident that the whole subject of hepatic stimulants must be studied anew, not by the older method of trying to ascertain their action on the organ as a whole, but rather on the cells which compose it. As I mentioned in my first lecture, the latest development of pharmacology is the “pharmacology of the cell;” and to it we must look for the fullest information regarding the action of remedies, whatever be the class to which they belong.

Fig. 6.—Action of toluene on active liver. Rabbit 6 weeks old. Last food, 6.30 hours before death. Toluene, 1 minim, 5 hours before death.

Time will not allow me to enter upon the relations between the chemical structure of remedies and their action upon other glands than the liver, and especially upon the kidneys. Nor can I even flatter myself that I have treated any part of my subject fully. All I have done is to attempt to give a brief outline of it, not discussing it with a view to completeness, nor always bringing prominently forward those points which would be most interesting to a chemist, but rather endeavouring to bear in mind the practical intention of these lectures, and to show as much as possible the relationship of my subject to the prevention, control, and cure of disease. In trying to do this, I have thought it advisable to look forward as well as backward, and to indicate lines of research on which work is desirable, even at the expense of time which might have been given to a fuller exposition of results already obtained. In conclusion, I must again return you my most cordial thanks, not only for the honour you have done me in selecting me to give these lectures, but for the patient and kindly hearing you have given them.

NOTES OF THREE CASES OF XERODERMA PIGMENTOSUM, OR DERMATOSIS KAPOSÍ.

By W. BROWN HUNTER, M.D.,
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In the number of the JOURNAL for June 8th there is a typical case of this disease well recorded by Dr. McCall Anderson. In a note to that report it is said that there are only forty-one cases of this disease recorded. I write this report chiefly for the purpose of adding three more cases to that record, two of which are certainly typical, and the third I have not seen, but for reasons given below its identity is undoubted. I enclose photographs of the two I have seen, and the third case was a brother of these, who is now dead. The family in which these cases occurred consists of eight children altogether, two of whom are dead, one a girl at the age of 2½ years, who was unaffected with the disease, and a boy aged 18 when he died, who was the eldest of the family