or two old; it is better to prepare it as required. The test solution should be mixed at the time of using. Any excess of sodium nitrite must be avoided, or a pseudo-reaction may be obtained. Neglect of this last precaution has led some observers to deny that the test has any diagnostic importance (Penzoldt, von Jaksch, Munson and Oertel, see below). The colour of the true reaction is a red, not orange or brown, and a pink froth is produced on shaking. It is a curious fact that in some cases, although the colour may be the right one, a white and not a pink froth forms; the reaction then is not a true one. The urine should be freshly passed and acid. It is only by attending to these minutiae that the test can take its proper place as a valuable diagnostic agent. Neglect of them brings failure and undeserved discredit.

The nature of the substance which gives the reaction is still unknown. It might be anticipated that cultures of the bacillus typhosus would give the reaction, but such is not the case. Like Dawson,⁶ who investigated this point, I have failed to get any trace of the reaction in broth cultures of the Bacillus typhosus. The bacillus employed for inoculation had been recently isolated, and the cultures were of various ages, from a day to a month. Cultures of a number of other organisms were also tested, namely, B. coli communis, B. anthracis, B. tetani, B. diphtheriae, B. prodigiosus, pneumococcus of Friedlaender, S. pyogenes aureus, streptococcus of erysipelas, Koch's comma bacillus, Finkler's comma bacillus, and Vibrio Metchnikovi, but in no instance was the reaction obtained. Penzoldt⁷ and Von Jaksch⁸ have stated that acetone is the substance which gives the reaction. Such is not the case, and these authors seem to have fallen into error by using a 5 per cent. instead of a 0.5 per cent. solution of sodium nitrite, and from the same cause Munson and Oertel⁹ believed that it depends upon aceto-acetic acid, but this is not so.¹⁰ I have tested the following substances to see if they give the reaction: caustic potash, sodium carbonate, ammonium sulphide, formic acid, zinc lactate, picric acid, salicylic acid, glucose, thymol, camphor, carbolic acid, oil of turpentine, asparagin, amygdalin, æsculin, santonin, salicin, brucine (three specimens), strychnine (three specimens), nicotine, caffeine, codeine, eserine, narcotine, piperine, cinchonidine, cinchonine, quinine, quinidine, papaverine, atropine, hyoscyne, and aconitine. All of these give only a yellow or orange, thymol a deep orange. Bagnacci¹¹ has stated that thymol, strychnine, and glucose give the reaction, but they certainly do not. Picro-sulphuric acid (Kleinenberg's) gives a brown colour.

The only substance I have met with which gives a reaction at all resembling the red typhoid reaction is morphine and its salts. The colour produced by morphine is very like a somewhat pale typhoid reaction, and the resemblance is the greater, as a pink froth is formed on shaking. It differs from the typhoid reaction, however, as no green precipitate forms on standing. The test is a very delicate one; 1 part of morphine acetate in 5,000 parts of water is readily recognised, and even 1 part in 10,000 can be detected. The reaction might perhaps be useful as a test for morphine. In connection with the diazo-reaction, the similar morphine reaction is of importance, because morphine is excreted by the urine, so that the urine of a patient taking this drug or opium might give a pseudo-reaction simulating the true typhoid reaction.

A PRELIMINARY COMMUNICATION ON THE FATE OF MICRO-ORGANISMS IN INSPIRED AIR.¹

BY
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[ABSTRACT.]

IN a communication we recently had the honour of reading before the Royal Medical and Chirurgical Society² on "Micro-

organisms in the Healthy Nose," we estimated that at least 1,500 organisms are inspired every hour, while it must be a common event for this number to rise to 14,000. In spite, however, of the enormous number of organisms inspired, numerous observers have shown that expired air is practically free from microbes (Tyndall, Gunning, Strauss). In the experiments of Strauss,³ of 609 microbes inhaled only a single one was expired. Lister's observations on pneumothorax caused by wound of the lung by a fractured rib seem to show that the organisms are arrested before they reach the air cells; while the experiments of Hildebrandt⁴ indicated that this arrest takes place before the trachea is reached, probably in the nasal cavities. This seems to be the case, for we have examined bacteriologically the tracheal mucus from many recently killed animals, and have always found it sterile. In our paper referred to above, we arrived at the conclusion that the mucous membrane of the normal nose seems to be usually quite free from micro-organisms, while the vestibules, vibrissæ, and crusts are swarming with them. If, then, the bacteria in inspired air are arrested in the nasal cavities, what becomes of them, and how are they got rid of? That the action of the ciliated epithelium is an important factor can hardly be doubted, for any particles deposited on a ciliated epithelial surface are rapidly moved onwards, as can be demonstrated by watching the movement of a particle of wet cork placed on the dorsal wall of a frog's pharynx.

The following experiment shows that bacteria deposited on the Schneiderian membrane are rapidly removed. Cultures were prepared from the vibrissæ and mucous lining of the nose of one of us who acted as the subject. No red growth developed in these, so that the bacillus prodigiosus was absent. A looped needleful of a pure culture of the bacillus prodigiosus was then deposited on a spot on the septum naris, and cultures were made from this spot and its neighbourhood at intervals up to two hours. Cultures made within 5 minutes gave an abundant confluent growth of bacillus prodigiosus; after 15 minutes the amount of growth was distinctly decreased; after 60 minutes the growth was diminished by 75 per cent.; after 80 minutes frequently no growth occurred; while after 2 hours no trace of the bacillus prodigiosus could ever be detected.

Wurtz and Lermoyez have stated that the nasal mucus exerts a bactericidal action, but so far we have been unable to confirm their researches.

We have made a number of experiments to test the bacterial condition of the air before and after passing through the nose. Our first experiments were very conflicting, but having perfected our methods, our later ones show that nearly all the organisms are arrested before reaching the nasopharynx.

We conclude that many of the organisms are arrested by the moist meshwork of the vibrissæ, while those which reach the mucous membrane are eliminated by the action of the ciliated epithelium, and by the trickling of the mucus. The mucus, from our experiments, seems to be an unsuitable nutrient medium, and the multiplication of organisms is thereby prevented. Phagocytosis may occur, but only to a small extent.

THE EXPERIMENTAL EVIDENCE CONCERNING THE PRODUCTION OF A HÆMATOGENOUS JAUNDICE.*

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FOR some time past my attention has been a good deal occupied in an examination of the evidence which in recent years has been advanced in support of the view that a hæmatogenous jaundice is no longer admissible. We may have a non-obstructive jaundice, which is by no means hæmatogenous, except in so far as the hepatic disturbance is initiated by changes in the blood. But a true hæmatogenic jaundice, or that produced exclusively from the blood, is regarded as

⁶ *Dub. Journ. Med. Sc.*, vol. xcv. 1893, p. 490.

⁷ *Berlin klin. Woch.*, 1884, No. 14.

⁸ *Clinical Diagnosis*.

⁹ *Med. Jour. (New York)*, vol. lviii. 1893, p. 127.

¹⁰ A. S. Warthin, *Med. News* (Philadelphia), vol. lxiii, 1893, p. 569.

¹¹ See Warthin (*loc. cit.*, note 10).

¹ Read in the Section of Pathology at the Annual Meeting of the British Medical Association, held in London, July-August, 1895.

² *Trans.*, vol. lxviii, 1895.

³ *An. de l'Inst. Pasteur*, 1888, No. 4.

⁴ *Ziegler's Beitr. z. path. Anat.*, Bd. ii, 1888, p. 421.

* Read in the Section of Pathology at the Annual Meeting of the British Medical Association, held in London, July-August, 1895.

having been disproved by certain experimental investigations, physiologists now holding that all forms of jaundice are of hepatic origin or due to reabsorption of secreted bile. In order to the examination of this evidence it will be necessary briefly to recount and review the observations which led up to the hypothesis of a hæmatogenous jaundice. Before doing so, however, it may be well to mention that the presence or absence of bile acids in the urine as a means of diagnosis between different forms of jaundice has been shown to be untenable, and therefore the question need not be taken notice of any further. It may also be advisable to preface the fact—possibly lost sight of by some—that the bile does not pass directly into the blood vessels of the liver in cases of obstructive jaundice. It was shown by Kufferath¹ that if both the thoracic duct and the common bile duct be ligatured none of the constituents of the bile passed into the blood; and in a beautiful investigation by Vaughan Harley² it was conclusively shown that under similar conditions no biliary constituents are to be found in the urine, even after the lapse of two or three weeks. After the lapse of some days supplementary ducts formed below the seat of ligature. Hence the path of the bile into the blood is *via* the lymphatics of the liver and the thoracic duct.

THE VIEW THAT JAUNDICE MAY BE CAUSED BY THE REABSORPTION OF SECRETED BILE FROM THE INTESTINE.

This is a view which modern investigation compels us to set aside. It was originated by Frerichs³ (and supported by Murchison) who thought he had shown that the bile acids when injected into the blood become converted into bile pigments. As the result of such injections in dogs, there was jaundice, and the urine contained bilirubin. Normally, according to this theory, the bile acids after absorption become first of all converted into bile pigments, and thence by oxidation into substances no longer endowed with the properties of bile pigment. An arrest of this oxidising process would, according to Frerichs, cause the accumulation of bile pigments in the blood, and so give rise to jaundice. Such he supposed to take place as the result of certain febrile processes.

It may be remarked that the pigments of secreted bile are reduced, and partly excreted with the fæces, as hydrobilirubin, and partly by the urine, as urobilin. The bile acids are mainly reabsorbed, not by the radicles of the portal vein, as some have supposed, but by the absorbents of the jejunum and ileum, and so pass into the thoracic duct. This reabsorption of the bile acids has a very pronounced effect on the secretion of the bile, as the experiments of Schiff⁴ have so conclusively proved. In dogs with biliary fistulæ, if the bile flowing from the fistula be introduced through a duodenal fistula, the secretion of the bile is soon notably augmented, and the same result is obtained if the portal vein be ligatured. A consideration of what follows will show that such reabsorption of bile acids is never, so far as we know, a cause of jaundice.

KÜHNE'S THEORY OF HÆMATOGENOUS JAUNDICE.

The phenomena observed by Frerichs after the injection of bile acids into the circulation received, as is well known, a very different interpretation from Kühne.⁵ He maintained that the effect of the bile acids was to cause a dissolution of the red blood corpuscles within the vessels, and from the hæmoglobin thus liberated he traced the bilirubin excreted with the urine. This supposition also fitted in well with the discovery by Virchow of the identity of bilirubin and hæmatoidin, an observation which has received ample confirmation from modern research. Kühne extended his observations and also produced bilirubinuria in dogs from injection of hæmoglobin into the circulation, and Tarchanoff⁶ showed that in dogs with biliary fistulæ the injection of either oxy-hæmoglobin or bilirubin into the circulation is followed by a greatly increased secretion of bilirubin by the liver, in addition to its appearance in the urine. Others confirmed these results, and various poisonous agents were discovered to produce this bilirubinuria; for example, arseniuretted hydrogen, toluylendiamin, chloroform, etc. (icterogenic drugs). These experimental results were applied to explain certain obscure cases of jaundice in man, wherein no obvious obstruction could be made out; for example, acute yellow atrophy,

pyæmic jaundice, phosphorus poisoning, and the jaundice of certain fevers. In all such it was held that the red blood corpuscles suffered disintegration within the blood vessels (hæmocytolysis) outside the liver, the hæmoglobin passing into the plasma and undergoing conversion into bilirubin within the circulating blood. Hence arose, on what seemed solid enough grounds, the modern conception of a hæmatogenous jaundice.

OVERTHROW OF KÜHNE'S THEORY: THE WORK OF MINKOWSKI AND NAUNYN.

It might indeed be supposed by a critical onlooker that such facts as have been stated could not be regarded as affording conclusive evidence for a hæmatogenous jaundice, seeing that the rôle of the liver under these circumstances was not minutely considered. For, although bilirubin was excreted in the urine, it was possible that the liver was not passing all its excreted bile into the intestine or fistula as the case might be. It was conceivable that under the altered circumstances a portion of the bile might effect an abnormal passage and enter the blood. And although the injection of bile acids or hæmoglobin caused bilirubinuria in the case of dogs, Naunyn,⁷ Steiner,⁸ and Legg⁹ were unable to obtain this in the case of rabbits. By the injection of these agents into the circulation of rabbits, these observers found well-marked hæmoglobinuria, but no bilirubinuria.

But the fatal blow was given to Kühne's theory by the experiments of Minkowski and Naunyn.¹⁰ Taking advantage of the "renal-portal" circulation which obtains in birds, they found that the flow of urine continued after ligature of the vessels of the liver. It may be remarked that Stern¹¹ had previously shown that in doves in which the vessels and bile ducts are tied, no biliary substances accumulate in the blood, while Moleschott¹² and others had long ago shown that extirpation of the liver in frogs was followed by entire absence of bile constituents from the fluids and tissues of the body. (Leyden, however, after tying the common bile duct in frogs, obtained no jaundice after fourteen days.)¹³ But Minkowski and Naunyn advanced their experiments a stage further, selecting for their purpose ducks and geese. On causing these animals to inhale arseniuretted hydrogen for a few minutes, bilirubin soon made its appearance in the urine. In one duck the urine gave Gmelin's reaction in six hours, and continued to do so for some days. In another duck, just as this bilirubinuria was at its full development, they extracted the liver. The result of this was severe hæmoglobinuria and a distinct fall in the bilirubin excreted. This fall continued until after the lapse of five hours, when at the death of the animal there was no trace of bilirubin or biliverdin either in the urine or in 35 c.cm. of blood. Again, in the case of geese, they excised the liver in one, and after it had so far recovered from the operation, subjected both it and a control goose to the action of arseniuretted hydrogen. The control goose soon passed icteric urine, while the liverless goose discharged in half an hour hæmoglobin-urine. It died in three hours, and after death hæmoglobin-urine was found in the cloaca. In other two geese arseniuretted hydrogen was first administered, and in an hour or two the urine was icteric. The livers were then extracted, and the animals survived for about three hours. Before death the urine was free from bile in one case, but contained much hæmoglobin; while in the other the bile was fast diminishing and could not be detected in the blood. These experiments, then, conclusively show that the jaundice which immediately follows acute poisoning with an icterogenic drug is not due to the formation of bilirubin within the blood, but is solely dependent on the liver.

THE OBSERVATIONS OF STÄDELMANN, AFANASSIEW, AND HUNTER.

In like manner Städelmann¹⁴ and Afanassiew¹⁵ constantly produced jaundice in dogs by means of toluylendiamin. In this jaundice there are two well-marked stages: First, there is a polycholia or increased flow of bile, which lasts on an average from three to eight hours, during which the jaundice begins to make its appearance. This is succeeded by an acholia, the flow of bile gradually diminishing, until by about the second day it may apparently cease to be secreted. During this stage the jaundice is at its height, and is alleged to be due to an inspissation of the bile in the

ducts. It is, in point of fact, an obstructive jaundice. Afanassiew, however, describes in these cases a sort of interstitial hepatitis whereby the blood vessels and lymphatics are dilated and the fine bile ducts compressed and choked. Hunter,¹⁶ from actual observation, denies this sequence of events, and he finds the viscosity of the bile to be due to congestion and catarrh extending from the bile ducts down into the duodenum. This catarrh he considers due to the irritant action of a substance or substances excreted with the bile, and as a result the lumen of the duodenum is filled with a clear, viscid, inflammatory mucus, free from bile pigment. I may say that I have myself obtained corroborative evidence of this under certain circumstances, as will subsequently be alluded to, and I should consider the viscosity of the bile in the ducts in all such cases to be due to the admixture of increased secretion from the glands of the ducts, as we know that bile when freshly secreted is always fluid, deriving its natural viscosity from the subsequent addition of a nucleo-albumin present in the secretion of the ducts and gall bladder.

A NON-OBSTRUCTIVE HEPATOGENOUS JAUNDICE.

It will be seen from the foregoing remarks that poisoning by toluylendiamin causes, in dogs at least, an obstructive jaundice, but we have also to face the fact that this obstruction is not always found, for jaundice occurs during the polycholia in dogs, when the bile flows freely into the intestine, and in the case of geese bile makes its appearance in the urine in half an hour after the administration of arseniuretted hydrogen. It is probable therefore that the disturbance induced by the poisonous agents is such as to cause a partial deflection of the bile over into the lymphatics, and so on into the blood. How else can the jaundice be accounted for? We may conceive, indeed, how the great demand made on the hepatic cell in respect of its bile-producing function would entail the arrest of glycogen formation. The equilibrium, so to speak, of the cell would be so disturbed as to lead to a dual current of the bile.

Here it may be remarked that the belief consequent on these experiments that all cases of jaundice were of hepatic origin, and due mainly to obstruction, has led, in an unwarrantable degree, to the adoption or readoption of various alleged mechanical causes as the explanation of certain obscure cases of jaundice in man—such as swelling of the hepatic cells, distension of hepatic capillaries, oedema of the capsule of Glisson (Birch-Hirschfeld), desquamation of the epithelium of the ducts (Buhl, Cornil, etc.), mucous exudation into the ducts, etc. Any of these factors, in addition of course to inspissation of bile, would serve to hinder the descent of the bile through the finest ducts, and so precipitate jaundice.

In examining a large number of human livers I was, however, forced to conclude that these mechanical conditions (excepting, of course, inspissation of bile) are rarely found sufficiently distinctive to warrant their adoption as foremost causes of jaundice. Oedema of the capsule of Glisson is not accompanied by jaundice, neither is swelling of the hepatic cells, nor yet dilatation of the hepatic capillaries. Ernest H. Starling¹⁷ has convincingly shown, in experiments on dogs, that the great increase of lymph observed after obstruction of the inferior vena cava above the diaphragm is entirely derived from the liver. I am informed by Dr. Starling that the lymph so obtained is not stained with bile pigment, so far as he observed. Hence, if oedema of the liver were a cause of jaundice, the latter could not fail to be a marked feature of these experiments. Again, mucous exudation into the bile ducts is, so far as I have observed, most prominently associated, in the case of the smaller ducts, with arrest of the normal flow of bile downwards from the bile capillaries, the normal discharge of mucus continuing. By some of the less recent writers, for example, Dr. George Harley,¹⁸ such accumulations of mucus, when associated with jaundice, were regarded as conclusively showing that the liver failed to abstract the bile from the blood, as they were unaware that reabsorption of secreted bile could occur high up, as well as from the larger biliary passages. I believe, however, that in all cases of jaundice from obstruction the passage of the bile into the lymphatics occurs chiefly, if not exclusively, in the bile capillaries and smallest ducts. In all these cases, then,

where no palpable obstruction can be traced, apart from the conditions which have just been discussed, the jaundice is in all probability to be attributed to a vital disturbance in the hepatic cell, such as I have described.

In this connection, mention may be made of the view which assigns certain cases of jaundice—for example, from mental emotion, icterus neonatorum—to lowering of the blood pressure in the portal vessels, the bile thereupon being induced to flow in the direction of least resistance, or into the blood. But this view, which originated with Frerichs, was supported by erroneous suppositions. He supposed, for instance, that the secretion of the bile was an act of filtration, which we know it is not, as the pressure at which the bile is secreted is, on an average, two and a-half times greater than that of the blood in the portal vessels; and, again, the pressure of the portal blood is subject to much periodical variation which is regulated chiefly by conditions of diet and fasting.

THE AUTHOR'S EXPERIMENTS: ACUTE POISONING WITH PHENYLHYDRAZIN.

With the object of obtaining, if possible, a more definite idea of the phenomena, both general and microscopic, which characterise the action of an icterogenic agent, I undertook a number of experiments, advisedly using for this purpose rabbits. For, as previously mentioned, bilirubinuria quickly makes its appearance in dogs subjected to the action of toluylendiamin, or when bile acids or oxyhæmoglobin are injected into their circulation. It is a curious fact, however, that no such result is produced in the case of rabbits. A hæmoglobinuria results from acute poisoning with the latter agents, but toluylendiamin has not even this effect. Toluylendiamin does not seem to injure them in any obvious degree; they live and thrive under large and frequently-repeated doses. I tried them with metaphenylendiamin, but they seemed little the worse for it also. There is an agent, however, which in my hands has acted admirably in their case, for by it one can produce the most diverse results by simply altering the dose, and that is phenylhydrazin.

In the first place, by a fairly large dose, subcutaneously administered, an acute poisoning was induced, death occurring in from twenty-four to thirty-six hours. An intense hæmoglobinæmia is in this way produced, the urine being charged with hæmoglobin. No trace of bile pigment can, however, be detected in the urine. Examination of the liver revealed considerable distension of the gall bladder, with hæmoglobin-stained bile, the latter being somewhat of a reddish colour (hæmoglobinocholia). This bile was perfectly fluid, and had a free exit into the duodenum, which contained a considerable quantity of bile-stained stuff. There was no appearance of catarrh. The intestines also contained a considerable quantity of this brown bile. On section, the liver excluded a thin serous fluid, which, though pale at first, soon acquired a red tinge from admixture with blood oozing from the hepatic veins. The spleen was much enlarged, fairly firm, and intensely congested. It would seem, in point of fact, that this hæmoglobinæmia is characterised by a great determination of blood to the viscera.

Under the microscope the liver showed nothing of much moment; the nuclei of the cells seemed, however, to be much stimulated. The blood in the capillaries was hardly to be distinguished from normal blood. The spleen was intensely full of blood, many of the corpuscles seemed to be disintegrating within the cells of the pulp, and a certain quantity of pigment was present. The capillaries of the lung were highly swollen with blood. The kidneys showed extreme vascularity of the glomeruli, with occasional hæmorrhages into the capsular space. The lumina of several of the cortical tubes were filled with blood. The urine was, as stated, saturated with hæmoglobin, and it deposited epithelium, some red blood corpuscles, and red granular matter which I took to be fragments of blood corpuscles.

SUBACUTE POISONING WITH PHENYLHYDRAZIN.

In the next place, a subacute poisoning was induced by administering small doses of the drug from day to day for a period of about eight days. On one or two days no injection was given. In these cases the *post-mortem* appearances were as follows: The duodenum contained much green-stained stuff; the gall bladder was well filled with a dark olive green,

but perfectly fluid, bile; and the hepatic, cystic, and common ducts were likewise well filled with a similar bile; the duodenum was bulged into a distinct pouch just opposite the entrance of the common duct, and, in one case, in which the animal had been kept exclusively on a diet of bread and milk, this pouch contained a bile-stained mucus of extraordinary viscosity, adhering with such tenacity to the wall that it could with difficulty be torn away. Herein we find a corroboration of the observation of Hunter formerly referred to. The liver on section became bathed with a serous fluid which, as in the former cases, got tinged by blood from the hepatic veins. The spleen was much enlarged and fairly firm. The urine gave a distinct Gmelin's reaction. As the microscopical disclosures in these cases are of great interest and importance, I shall discuss them alongside those described by Minkowski and Naunyn.

MICROSCOPICAL APPEARANCES: CRITICAL COMPARISON WITH THOSE DESCRIBED BY MINKOWSKI AND NAUNYN.

These authors have described and figured the minute changes in the liver, spleen, and bone marrow in the subjects of their experiments. By special methods of preparation, chief of which is hardening of the fresh tissue in a 5 per cent. solution of corrosive sublimate for 24 hours, they found within the smaller blood vessels and capillaries of the liver, large cells enclosing red corpuscles, and similar cells enclosing disintegrating corpuscles and the brown-red pigment of Langhans, or else this pigment in association with a bright or grass-green pigment. They also found these cells in the spleen and bone marrow, but in these instances without containing the green pigment. The cells were not to be found in the general circulation. These cells in the liver, moreover, were rich in iron. The green pigment in these was either pretty uniformly diffused throughout the cell, or else it was confined to one portion of the cell, the rest of the protoplasm containing the Langhans pigment. They affirm the green pigment to be true biliverdin, and to be derived from the ultimate disintegration of the blood corpuscles within these large cells, expressly stating that the green coloration is not derived by imbibition of bile. By the sublimate method they allege that they could detect the hæmoglobin passing into bile pigment. Clumps and granular masses of biliverdin were also conspicuously seen in the hepatic cells proper and in the bile ducts, and in that portion of the hepatic cell nearest the bile capillary were numerous granules, which gave a strong iron reaction. In dogs poisoned with toluyldiamin they also saw the corpuscle-holding cells, but in much fewer numbers, and without the green pigment. Finally they conclude that these appearances are merely an exaggeration of what is normally found in the liver of ducks and geese; in a normal goose which was the subject of a polycholia beyond that usually seen, they likewise found these cells to be present in the liver.

Now I shall describe the microscopic disclosures after subacute poisoning by phenylhydrazin in rabbits, where death occurred from about the sixth to the ninth day. For hardening I employed Flemming's solution, Müller's fluid, alcohol, and also the sublimate solution. For staining purposes the Biondi-Ehrlich reagent answered best, as by it the red blood corpuscles in particular were sharply differentiated from the various pigments resulting from their destruction, which retained their natural colours. In the small vessels of the portal vein within the liver I saw some leucocytes containing pigment particles, which were generally of a golden yellow colour, but sometimes of a greenish tinge. In addition to this, there was a considerable quantity of free pigment in the vessels. I never saw any cells contain blood corpuscles. In a great many of the capillaries were pigment masses, either golden yellow or bright green. These pigments were seen both existing together and likewise apart from each other. The stellate cells of Küpffer were not infrequently mapped out by the pigment. The hepatic cells themselves were well charged with pigment granules, always of a brownish yellow colour. Their nuclei were large and not infrequently showed mitotic change. The liver cells, moreover, showed no marked degenerative changes; they were apparently actively secreting, and the bile ducts contained bile. The spleen was vastly charged with blood, and great numbers of the endothelial cells of the pulp, and apparently also leucocytes, were crammed

with pigment and disintegrating red corpuscles. In many of these cells the pigment was of a grass-green colour. The cells of the bone marrow gave in a great majority the methyl-green tint with Biondi's reagent. But little pigment was found, not more than was compatible with a normal condition of affairs. No pigment was observed in the kidney.

In comparing the results with those of Minkowski and Naunyn, I think one is justified in holding that they represent very much the same state of matters. The only differences consist in the blood corpuscle-holding cells in the liver and the alleged absence of green pigment from the spleen in their cases. I do not know if these are to be accounted for by the considerable difference in the duration of the poisoning or by the difference in species. I am inclined, however, to throw grave doubt on the assumption by these authors that the green pigment in the vascular cells of the liver is specifically formed there, and denotes the passage of hæmoglobin into biliverdin. For this would imply a formation of biliverdin apart from the specific action of the liver cell. It is difficult to see how the mere fact of these cells being within the liver capillaries could confer any specific action on them. Again, we have to consider that biliverdin is an oxidation product of bilirubin. The fact that the bright green pigment was undoubtedly present in the spleen in the case of rabbits adds a still more serious blow to their assumption. The green pigment would seem in point of fact to be a precursor of the yellow, or, in other words, these pigments illustrate the reduction of hæmatin.

THE SEAT OF THE BLOOD DESTRUCTION.

In judging of the quantity, character, and situation of the pigment found within the liver, and comparing the same with that found within the spleen, the conclusion which irresistibly forced itself on my mind was that the liver was deriving all its pigment from the spleen. In the latter the pigment was so greatly in excess of that found in the liver, and the fact that the spleen was also visibly manufacturing pigment at a great rate left but little room for doubt in the matter. I do not deny the inclusion of red corpuscles by cells in the hepatic veins in Minkowski and Naunyn's cases, but have these observers shown whence these corpuscle-holding cells are derived? On the other hand, in the present experiments, while no active dissolution of corpuscles could be detected in the liver, this was plainly manifest in the spleen. It has commonly been supposed that the pigment is formed in the general circulation, the spleen and liver merely serving as traps to catch up the pigment or pigment-carrying leucocytes as they pass through. This is erroneous. The pigment is not formed within the circulating blood at all. I may go further, and affirm that under similar circumstances pigment is never formed within the circulating blood. It is formed in the spleen. Great numbers of the endothelial cells of this organ may be seen holding the corpuscles in all stages of downward metamorphosis. Hunter, in his classical researches on pernicious anæmia, has clearly underrated this function of the spleen, but very recently Dr. Hunter kindly drew my attention to his most recent investigations on blood destruction,¹⁰ wherein I find that he has abandoned his former position, and gives practically the whole credit to the spleen. He has proved this by toluyldiamin experiments. With small doses of this substance the "morphological changes indicative of hæmolytic are confined solely to the spleen and the blood of the splenic vein," while "after removal of the spleen the destructive action of toluyldiamin on the blood of rabbits, in doses both small and medium, is completely abolished." So he says, "I cannot interpret these facts in any other way than by concluding that the spleen has been the chief seat of this hæmolytic, and that the sole part the liver took in it was to dispose of the products." There can therefore be no longer any doubt that the hæmocytoysis (as I should prefer to call it) is effected by the spleen, and the products, or at least the soluble products, are carried over to the liver to be excreted by that organ as bile pigments. In these cases of Minkowski and Naunyn's, as likewise in my own, the great increase of work thus thrown on the liver is the cause of the unusual production of bile, by the inspissation of which or otherwise a jaundice was brought about. It now remains to be seen whether this is the conclusion of the whole matter.

THE EFFECT OF PROLONGED POISONING WITH PHENYLHYDRAZIN ASSISTED BY METAPHENYLENDIAMIN.

Having determined the action of large and moderate doses of phenylhydrazin, I finally endeavoured to induce a prolonged poisoning with this agent. The best results, however, were obtained by first administering fairly large doses of metaphenylendiamin for about a week or ten days. An inconvenience attendant on the subcutaneous administration of this agent sometimes occurs in the shape of necrosis of the skin at the seat of the injection. Barring this, it is not followed by appreciable ill-effects on the health of the animal. It causes, however, as Hunter has shown in the case of toluylendiamin (in rabbits), a considerable destruction of blood corpuscles in the spleen, though this is not followed by hæmoglobinuria (unless given in enormous doses), nor yet by the presence of bile pigments in the urine. After the treatment by metaphenylendiamin, the phenylhydrazin was given in small daily doses, occasionally omitting a day or two days. Generally in from eight to twelve days the symptoms became serious, œdema being not infrequently seen conspicuously about the head. By sinking vessels in the floor of the receptacle in which the animals were confined, the urine was generally regularly obtained for examination. Two or three days before the urine gave Gmelin's reaction the conjunctivæ were seen to be somewhat jaundiced in one case. By this method of poisoning, after the lapse of about eighteen days the urine will begin to give Gmelin's reaction, but considerably less marked than in the cases of subacute poisoning after eight days. Typically, the *post-mortem* appearances in such cases were as follows: On opening the body, there was considerable œdema, generally at least in the form of some ascites. The blood had a marked "laky" appearance and consistence, and quickly coagulated, both in the vessels and outside of them. In the case of the liver, coagula were sometimes found in the portal veins which were evidently formed *ante mortem*. Under the microscope these thrombi in the liver had a hyaline appearance; there was no ordinary fibrin to be seen. Thrombosis is a well-known tendency of laky blood, and due, as Wooldridge²⁰ has demonstrated, to the excessive liberation of fibrinogen from the broken up stromata of the red corpuscles. The hæmoglobin contains no fibrinogen. The hyaline or homogenous condition of the thrombi has been described in particular by Recklinghausen²¹ as a peculiar modification of fibrin which occurs most typically after transfusion of blood from one species to another, as in the cases of lambs' blood transfusion into dogs and men given by him. The thrombi in question he ascribes to a local change in the walls of the vessels induced by the altered blood. In Wooldridge's experiments the portal vein was always the first seat of this clotting. The œdema also is to be explained by the results of Wooldridge's experiments. He found that injection of fibrinogen into the circulation of dogs causes extensive œdema of the leg if the femoral vein be ligatured, whereas in the normal dog ligature of the vein has no obvious effect.²² This œdema he attributes to a disturbed relationship between the blood and the vascular wall.

Examination of the liver in these cases revealed but a small quantity of bile in the gall bladder, which gave a flaky precipitate. No obvious catarrh of bile ducts or duodenum. The contents of the duodenum were bile stained but not viscid. A good deal of serum oozed from the liver on section—in fact, the organ generally seemed swollen from œdema. The spleen was greatly enlarged and extremely firm. The urine drawn from the bladder was generally of a dark brown colour. It gave the reactions for blood, albumen, and bile pigment. The sediment consisted of epithelial cells, granular casts, and cohering masses of granules.

Under the microscope the spleen was found to be enormously charged with pigment of a golden yellow colour. Even the Malpighian corpuscles were invaded by this pigment. Not a few of the cells, however, showed active hæmocytolysis still going on in their interior, and they gave a marked iron reaction. In the liver the portal vein and the capillaries were highly coloured by this pigment, carried over, as already shown, from the spleen. Many of the endothelial cells of the vessels, and likewise the cells of Kûpfer, were clearly mapped out by the deposition of the colouring matter; but the liver cells themselves were quite devoid of pigment; they were pale and in a condition of fatty degeneration, the proto-

plasm of the majority of them being transformed into fine oil or fat globules. On the other hand, the blood of the hepatic veins contained much pigment, and in the kidney these pigment granules were seen amongst the cells of the convoluted tubes, whilst the lumina of the straight tubes in the pyramids were frequently choke full of the same yellow pigment. Here then it was indisputable that the granular pigment brought to the liver from the spleen was carried over in abundance into the general circulation, and, if so, can there be any doubt that pigment existing in soluble form in the blood plasma was also carried over?

THE IDEA OF A HÆMATOGENOUS JAUNDICE NOT TO BE DISCARDED.

Now, whereas in the experiments of Minkowski and Naunyn, as also in the second series here described, the liver was found to be most actively engaged in disposing of the products of the blood destruction, we have just seen that a further stage may be reached in which the liver apparently refuses any longer to deal adequately with those products, its cells undergoing degeneration. The result of this is that the pigments of reduced hæmoglobin will be carried beyond the liver into the general circulation, stain the tissues, appear in the urine, and so bring about a true hæmatogenous jaundice. In order, then, to the production of such a jaundice, two factors are brought into play. One is an excessive destruction of blood in the spleen, a destruction which has advanced to a stage and to an extent far beyond that found in a mere temporary hæmoglobinæmia, such as that produced in liverless geese and ducks. In hæmoglobinæmia we have the hæmoglobin passing into the urine as such; but here we have one point to remark on, and it refers to certain experiments by Hunter with respect to the action of toluylendiamin.²³ He alleges that in poisoning with this agent the hæmoglobin is not excreted as ordinary hæmoglobin, but enters into combination with a substance or substances contained in the blood plasma, in such a manner as to cause it (the hæmoglobin) to assume a particulate form, and appear in the urine in the form of yellow discoidal bodies, like ordinary red corpuscles. Of this I cannot speak, but would remark that it is not to be confounded with the excretion of pigment through the kidneys which I have described. The second factor is an inefficient or paralytic condition of the liver cells so far as the excretion of bile pigments is concerned. We may even conceive, however, of a partial action of the liver which, nevertheless, does not prevent the escape into the circulation of a large proportion of hæmochromogen and its decomposition products. Thus we might have presumably a combination of the two forms of jaundice.

It seems to me, therefore, that we cannot regard the experiments of Minkowski and Naunyn as finally disposing of the doctrine of a hæmatogenous jaundice. They have done a great service, however, in disproving the hitherto recognised hypothesis of such a jaundice. They have also been of indispensable assistance in helping on to a different conception of what a true hæmatogenous jaundice may be, should there be anything in the observations which I have endeavoured, very imperfectly, yet not, I trust, unfaithfully, to represent.

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- ² BRITISH MEDICAL JOURNAL, 1892, vol. ii, p. 397, and Du Bois Reymond's *Archiv*, 1893, p. 291.
- ³ *Treatise on Diseases of the Liver*, p. 91 et seq.
- ⁴ *Pflüger's Archiv*, vol. iii, p. 598 et seq.
- ⁵ *Virchow's Archiv*, vol. xiv, p. 310.
- ⁶ *Pflüger's Archiv*, vol. ix, p. 53.
- ⁷ *Archiv f. Anat. u. Phys.*, 1868, p. 410.
- ⁸ *Archiv f. Anat. u. Phys.*, 1873, p. 160.
- ⁹ *St. Bart's Hosp. Repts.*, vol. xii, pp. 28, 29.
- ¹⁰ *Arch. f. exper. Path. u. Pharmacol.*, Bd. 21, pp. 1-33.
- ¹¹ *Arch. f. exper. Path. u. Pharmacol.*, Bd. 19, pp. 39-59.
- ¹² *Arch. f. phys. Heilkunde*, 1852, p. 479.
- ¹³ *Beitr. z. Path. des Icterus*, 1866.
- ¹⁴ *Arch. f. exper. Path. Pharmacol.*, vols. xiv. and xvi.
- ¹⁵ *Virchow's Archiv*, vol. xcvi, and *Ueber Icterus*, etc., 1891.
- ¹⁶ BRITISH MEDICAL JOURNAL, August 20th, 1892.
- ¹⁷ *Journal of Physiology*, vol. xvi, p. 224.
- ¹⁸ *Diseases of the Liver*, 1883.
- ¹⁹ BRITISH MEDICAL JOURNAL, December 3rd, 1892.
- ²⁰ *Chemistry of the Blood*, 1893, p. 167.
- ²¹ *Handb. d. allgem. Path.*, pp. 134, 135, 413, 414.
- ²² *Ibid.*, p. 350.
- ²³ *Lancet*, October 6th, 1888.

Dr. WILLIAM HUNTER congratulated the author on the interesting results he had obtained. He found himself in agreement with Dr. Auld's observations on so many points, that the only contribution he could make to the discussion would be rather of the nature of detail. In particular he agreed as to the importance of the spleen as a seat of blood destruction. He would only point out that if, as the author

concluded, bile pigment could be formed in the spleen apart from the liver, his results rather lent support to the doctrine of a hæmatogenous jaundice, for the very essence of that view was that bile pigment could be formed from hæmoglobin apart from action of liver cells.

Dr. AULD, in reply, said that in regard to the question put by Dr. Hunter, it seemed to him that the hæmatogenous jaundice he had described corresponds to the jaundice brought about by the absorption of the decomposition products of a large extravasation of blood. This was of admittedly frequent occurrence, and the excreted hæmatoidin gave the reaction for bilirubin. The destruction of blood he had described in the spleen gave rise to the same pigmentary products as in the case of extravasation.

ON THE OCCURRENCE OF A CANCEROUS DEVELOPMENT IN SIMPLE ULCER OF THE STOMACH.*

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In a former article¹ I have briefly referred to some few points in the morbid anatomy of gastric ulcer which seem to have a direct clinical bearing on such cases. In the present communication I wish to draw attention solely to one event, which, although rare, is undoubtedly of importance to both physician and surgeon, namely, the cancerous development of a "simple" or so-called "round" ulcer of the stomach.

EARLY REFERENCES.

The earliest writers to clearly draw attention to such a condition appear to have been Dittrich and Rokitsky.²

Brinton³ in 1856 wrote: "as respects the combination of gastric ulcer with cancer of the stomach they seem to be chiefly limited to a cancerous degeneration or deposit that involves the hard brawny mass which we have already noticed as generally present in variable quantity in the base or periphery of an ulcer of long standing. The most frequent form of such a combination appears to be that in which a fungus (generally a bleeding one) shoots up from the basis of a gastric ulcer, the characters of which are in all other respects those usually seen in the ordinary lesion."

Lebert⁴ also appears to have observed the direct transition from ulcer to cancer.

Waldeyer,⁵ according to Leube, seemed to believe that a process which at first is simply ulcerative may in time be converted into a cancerous one.

Hauser,⁶ too, according to Leith, had met with the evolution of cancer from the site of an old ulcer.

FREQUENCY OF OCCURRENCE.

The occurrence of cancerous development in the floor or edge of a simple gastric ulcer is undoubtedly extremely rare. So exceptional is the association that many authors, and amongst them Trousseau,⁷ Fox,⁸ and Fenwick,⁹ practically deny that it is ever met with.

Even Ewald¹⁰ lays no stress on the association, although he admits that "chronic ulcer of the stomach is one of the factors which favour the formation of cancer."

Strümpell,¹¹ however, ventures the exceptional opinion that "it is probably not a very rare event that cancer eventually develops in the floor of the old ulcer."

Eppinger¹² goes further, and volunteers the surprising statement that in 11.4 per cent. of cancers of the stomach development from an ulcer occurred. This is manifestly the outcome of fallacious statistics.

Welch¹³ states that "it may be considered established that cancer sometimes develops in a simple ulcer of the stomach." He also adds, "It is most likely to develop in large and deep ulcers with thickened edges, where complete closure by cicatrization is very difficult or impossible."

Fagge¹⁴ long since at Guy's Hospital noticed "more than one case in which the stomach presented part of the circum-

ference of what was apparently a simple ulcer, of which the remainder had been replaced by a malignant growth."

Dr. Norman Moore,¹⁵ in his analysis of cases of ulcer of the stomach occurring at St. Bartholomew's between the years 1867-1880, mentions no example of this association.

RECORDED CASES.

Exceedingly rare though this connection may be, some few cases have, however, been published. Brinton¹⁶ in 1857 recorded a case occurring in a woman, aged 41, in whom he considered "the gastric ulcer had undergone a cancerous infiltration or deposit." He also states that one or two similar specimens may be seen in the pathological museums of London. Meyer¹⁷ also describes a case where cancer developed in the immediate neighbourhood of an ulcer. Rosenheim¹⁸ believes that he has met with the combination in several instances. Leith¹⁹ records an undoubted example occurring in a man of about 48. Flatow²⁰ has met with cancer in a young man, aged 26, with a history of ulcer beyond doubt. Cases have also been placed on record by Lebert,²¹ Hauser,²² Heitler.²³

It is well to bear in mind that not infrequently cases of ulcer with firm cicatricial tissue, and which occasionally give rise to a distinct tumour, may very closely simulate cancer, as has been shown by Dr. Dreschfeld²⁴ and Professor Ewald. In the considerable number of cases of gastric and duodenal ulcers and carcinomata of the stomach which have come under my notice in the Pathological Department of the Manchester Royal Infirmary I have only met with the one case, recorded below, where the association of ulcer and cancer could be considered as undoubted. The following is also, I believe, the youngest case on record, except, perhaps, the instance mentioned by Flatow.

CASE.

*Clinical History.*²⁵—W. M., aged 27, member of a military band, was admitted to the Manchester Royal Infirmary on February 13th, 1894, under Professor Leech, to whose kind courtesy I am indebted for permission to here record this case. Patient had been abroad in the army for six years, spending the chief part of this time in Malta and Egypt. Four years ago, while serving as a bandsman at Malta, he commenced to be troubled with pain in the stomach, especially severe some time after meals. The pains gradually became worse, and were associated with pain in the inter-scapular region. Sour eructations and occasional attacks of vomiting occurred. Vomiting usually greatly relieved the pain. These gastric attacks had lasted for at least four years, but he had intervals, some shorter, some longer, when he was fairly well. Eighteen months ago he had a long interval of freedom from pain and vomiting for three months. He was considered to be the subject of a chronic simple ulcer of the stomach. Six weeks before admission to hospital the vomit was noticed to be dark and coffee-coloured. The pain and vomiting rapidly became much worse, and a distinct swelling in the region of the stomach was noticed. On admission a distinct tumour-like bulging was detected in the epigastrium and left hypochondrium clearly connected with the stomach. There was frequent vomiting, and on several occasions blood was brought up. Sarcinae were often found in the vomit. On many occasions washings from the stomach were examined for the presence of HCl, testing with congo-red and phloro-glucin-vanillin. It was usually present, but two or three times appeared to be absent. Special methods of feeding were employed, but the patient's condition did not improve. Surgical interference was deemed inadvisable. After becoming extremely emaciated death occurred on April 24th.

I made a *post-mortem* examination the following day. The following is an abstract of the report:

*Necropsy.*²⁶—Body that of extremely emaciated young adult male. On opening the abdominal cavity a few nodules of growth were found projecting from the serous coat lining the abdominal wall. No peritonitis. On lifting up the liver a mass of firm cicatricial-like tissue found to involve pyloric end of stomach. The stomach was small and contracted, and lying in greater part under cover of the liver. A tumour-like mass felt to be involving greater curvature and anterior wall near pylorus. Stomach closely adherent to under surface of left lobe of liver, and also attached across the longitudinal fissure to the left edge of the right lobe. On opening stomach along greater curvature, large ulcer exposed, situated immediately to the left of the pyloric orifice, involving smaller curvature and extending on to anterior and posterior walls. Size $3\frac{1}{2}$ by $1\frac{1}{2}$ inches. The edges were rounded, thick, indurated, and in parts undermined. The base of the ulcer was part formed by pancreas and peri-pancreatic tissue, but where it involved anterior wall of stomach its base was formed by the lower surface of the left lobe of liver, to which stomach was closely adherent. The base was very much thickened, chiefly by chronic inflammatory tissue, but in places there were nodules of growth. Immediately around the ulcer and involving its edges there were distinct nodules of malignant growth. The growth appeared to be extending from the edges and infiltrating the adjoining mucosa. The extent of ulceration was very considerable, while the amount of actual malignant tissue was relatively small. The pylorus was so close to the ulcer that it was considerably compressed, and its lumen much narrowed.²⁷ The liver was apparently uninvolved by any secondary deposits although closely adherent to the ulcer. The external coat of the gall bladder was slightly invaded by malignant growth, evidently from direct extension. The thoracic organs and remainder of abdominal viscera, except for marked wasting and anaemia, presented no gross lesions.

* Substance of a communication to the Section of Pathology at the Annual Meeting of the British Medical Association held in London, July-August, 1895.