THE ACTION OF TOLUYLENEDIAMIN : A CONTRIBUTION TO THE PATHOLOGY OF JAUNDICE.

PART I.

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(PLATE XVII.)

THE action of toluylenediamin has formed the subject of an extensive series of observations by Stadelmann; and this has been supplemented in various directions by Afanassiew, Noël Paton, and Engel and Kiener.

Stadelmann's observations relate to the nature of the jaundice produced by this drug, and more particularly to the intimate changes in the bile to which the jaundice is due.

Afanassiew's observations relate more particularly to its destructive action on the blood, and to the vascular changes it produces in the liver.

Noël Paton¹ made use of the drug in his observations regarding the relation of urea formation to destruction of blood.

Engel and Kiener² have studied more particularly the pigment changes in various organs following its destructive action.

The author's observations have related more especially to the action of the substance on the blood, the distribution of its destructive action in various parts of the circulation and in various organs, the channels by which it is excreted, and its action on the liver and on the bile ducts and duodenum in the course of its excretion.

The latter observations bear very directly on the pathology of the jaundice caused by this drug; and with these it is proposed to deal in this first part.

I. STADELMANN'S OBSERVATIONS.

In their entirety the researches of Stadelmann constitute the most important contributions to the pathology of jaundice that have been made within recent years.³

¹ *Journ. Anat. and Physiol.*, London, 1886.

² *Compt. rend. Acad. d. sc.*, Paris, 1887, p. 465.

³ "Das Toluylenediamin und seine Wirkung auf den Thierkörper," *Arch. f. exper.*

Their chief result is to show that a number of forms of jaundice, formerly regarded as of non-obstructive and hæmatogenous nature, are really of obstructive origin.

The result has been arrived at from a careful study of the changes undergone by the bile in forms of jaundice connected with an excessive destruction of blood.

Toluylenediamin poisoning.—Of special interest and importance in this relation has proved to be the study of one drug in particular—toluylenediamin.

This drug has the peculiar action, first noted by Schmiedeberg, of causing intense jaundice in dogs. Stadelmann, who, at Schmiedeberg's suggestion, undertook to investigate its action, was at first quite unable to explain the jaundice. He failed to find any evidence of duodenal catarrh; nor at first did he find that it had any destructive action on the blood.

Its action, however, occasions well-marked changes in the bile. In the first stage the bile is increased in quantity, and is very rich in bile pigments; this stage beginning about 2 hours after the injection, and lasting about 12 hours.

Then follows a second stage, during which it loses all the characters of bile, and is replaced by a small quantity of viscid, colourless mucus. This begins about the fourteenth hour, and lasts from 60–70 hours, after which the bile gradually returns to its normal character.

The jaundice begins during the first stage, reaches its maximum during the second, and gradually disappears during the third.

The jaundice is marked by the presence of bile acids in the urine, sometimes in abundant quantity. This increase of the bile acid does not occur contemporaneously with the increase in the bile pigments. On the contrary, they are usually diminished during the first stage, at the time when the bile pigments are increased. It is only about the twenty-second, thirty-first, or forty-eighth hour that they appear in the urine; they reach their maximum in the next 24 hours, diminish during the following 24 hours, and then disappear altogether.

Their appearance in the urine, therefore, does not correspond in point of time with the development of the jaundice, for the latter is well developed 15–20 hours after the injection, while the bile acids do not appear until later.

In one important particular Afanassiew¹ supplemented these observations by showing that the drug exercises a markedly destructive action

Path. u. Pharmacol., Leipzig, 1881, bd. xiv.; "Zur Kenntniss der Gallenfarbstoffbildung," *Ibid.*, Leipzig, 1882, bd. xv.; "Arsenwasserstoffvergiftung: Ein weiterer Beitrag zur Lehre vom Icterus," *Ibid.*, Leipzig, 1883, bd. xvi.; "Das Chronische Vergiftung mit Toluylenediamin," *Ibid.*, Leipzig, 1887; "Weitere Beiträge zur Lehre vom Icterus," *Deutsches Arch. f. klin. Med.*, Leipzig, bd. xviii.; "Ueber den Einfluss des experimentell in den Körper Eingeführten Hämoglobins auf Secretion und Zusammensetzung der Galle," *Ibid.*, Leipzig, bd. xxvii.; "Der Icterus und seine Verschiedene Formen." Stuttgart, 1891.

¹ *Ztschr. f. klin. Med.*, Berlin, bd. vi.

on the blood, an observation subsequently confirmed by Stadelmann himself.

This observation seemed to supply the missing clue to the explanation of the jaundice. That explanation, according to Stadelmann, is that the drug causes a destruction of blood; the hæmoglobin set free leads to an increased formation and excretion of bile pigments; this increased excretion is attended by an altered character of the bile in the direction of increased viscosity; this, in the face of the low pressure at which the bile is excreted, causes a temporary obstruction, and leads to a reabsorption of the bile; and when the action of the drug exhausts itself, the bile gradually loses its viscid character, the flow of bile is re-established, and the jaundice disappears.

In the case of this drug, then, it will be noticed that a jaundice which at first sight has all the character of a hæmotogenous jaundice depends upon intimate changes in the character of the bile, leading to a temporary arrest of its flow.

Phosphorus poisoning.—And similarly with a well-known form of jaundice, always regarded as a typical example of non-obstructive jaundice—phosphorus poisoning has been shown by Stadelmann to be due to similar changes, differing only in one respect, that they are slower in their production.

Ten hours after the administration of this poison, the bile begins to be darker in colour; the bile pigments are increased by one-half, the bile acids at the same time being diminished. For the next 24 hours these conditions persist, and no jaundice develops.

Then the bile begins to change its character; it becomes clearer, more mucoid; its quantity sinks to about one-fifth; the bile pigments fall to one-half or one-third their normal amount; and the bile acids fall to a very low amount, 0.1, 0.15, or 0.7, instead of the normal 1.96.

It is at this stage that jaundice develops; but it only reaches a maximum about 5 days after the administration of the poison.

As the jaundice disappears there is again an increased excretion of bile pigments, doubtless derived by reabsorption from the tissues.

The bile acids, however, remain diminished for some days longer; and it is not till the tenth or eleventh day that they again reach their normal.

Arseniuretted hydrogen.—A similar explanation applies to the jaundice occasionally produced by inhalation of arseniuretted hydrogen.

Stadelmann's observations show that the action of this is attended by a remarkable condition of concentration of the bile, the gall-bladder and bile ducts being filled with a thick viscid bile, which frequently contains large quantities of amorphous sediment, as well as numerous crystals of bilirubin. Hence he concludes that the jaundice is undoubtedly the result of absorption—hepatogenous and not hæmatogenous.

The increase in the bile pigments in the first instance was as great

as three and a half times its previous amount; and relative to the quantity of bile excreted it was still greater (twenty times), the quantity of bile being reduced five and a half times.

The bile acids, on the other hand, were reduced to as much as one-tenth their normal amount.

The relation of the various events to each other he conceives to be as follows:—"Without doubt the breaking down of the blood is the occasion for the icterus—but only through the agency of the liver, which produces an abnormal bile, in consequence of the abnormal blood conveyed to it."

II. CONSIDERATION OF FOREGOING RESULTS.

These observations are important, not only as serving to explain the action of the particular drugs, but still more in relation to the pathology of so-called "non-obstructive" jaundice generally.

The jaundice of phosphorus poisoning has long been held to be a striking example of jaundice unconnected with any obstruction—of a jaundice due to suppression. So also the jaundice connected with an excessive destruction of hæmoglobin, *e.g.* in burns and scalds (Klebs, Ponfick, Lassar); following the injection of water or hæmoglobin (Kühne, Tarchanoff); or the inhalation of ether and chloroform (Nothnagel); of poisoning with pyrogallie acid or naphthol (Neisser); of paroxysmal hæmoglobinuria, malaria, pernicious anæmia—has been held to be an example of a jaundice of hæmatogenous origin.

And yet for phosphorus itself, as well as for toluylenediamin and arseniuretted hydrogen, which both exercise a markedly destructive action on the blood, these observations would appear to show that the jaundice they severally occasion, differing as it does in respect of its intensity, rapidity of onset, and other characters, is in all cases the result of changes in the character of the bile, and is essentially obstructive in its nature.

Moreover, the very feature which was held to distinguish a jaundice of hæmatogenous from one of *obstructive* origin, namely, the absence of bile acids from the urine in the former, receives from these observations an entirely different explanation.

It has hitherto been assumed that the formation of bile pigments and bile acids by the liver cells must necessarily go hand in hand, and that an increase or diminution in the one must be accompanied by a corresponding increase or diminution in the other. On this assumption, the absence of bile acids from the urine at any time when bile pigments were present, was regarded as denoting that the bile pigments had been formed elsewhere than in the liver. Stadelmann's observations demonstrate for the first time that the two processes do not necessarily go hand in hand. On the contrary, a large excretion of bile pigments may be attended by a diminished excretion of bile acids, and conversely.

In no respect, indeed, are his observations, in my opinion, more striking than in the demonstration they afford of this fact; and Stadelmann himself attaches a special importance to it.

If then, as would appear, bile pigments can be formed by the liver cells without any corresponding formation of bile acids, the absence of bile acids from the urine in certain forms of jaundice need not necessarily denote, as has hitherto been supposed, inactivity on the part of the liver. On the contrary, it is quite compatible with increased activity on the part of that organ in transforming hæmoglobin into bile pigments, and with a jaundice of purely obstructive nature connected with the excretion of these bile pigments.

On this view, then, many forms of jaundice connected with disorder of the blood, hitherto regarded as of non-obstructive nature, must be grouped as varieties of obstructive jaundice—the occasion of the obstruction being intimate changes in the character and consistence of the bile, similar to those caused in phosphorus and toluylenediamin poisoning.

Stadelmann's Explanation of the Obstruction.

An important point, then, with regard to such forms of jaundice, is to understand how the blood changes are related to those in the bile which occasion the obstruction.

According to Stadelmann, the relationship is of this kind. The blood disorder is usually marked by increased destruction of blood; the increased supply of hæmoglobin to the liver occasions an increased formation of bile pigments, which is attended at the same time by an increased concentration of the bile, caused by the specific action of the poison on the liver cells; this change in the character of the bile suffices to cause temporary obstruction to the flow of bile (with jaundice). The most constant and important change he regards as the increased formation of bile pigments (polychromia), so much so, that in his opinion the jaundice might most fitly be termed "jaundice from polychromia."¹

He takes strong exception to the term "polycholia" in this relation, as fitly describing the character of the jaundice. He contends that the term polycholia can only be rightly applied where there is an increase of all the constituents of the bile, both watery and solid. And, as he points out, this is not the case in the forms of jaundice now under consideration. So far from the quantity being increased, it is often diminished from the very first; and so far from the bile salts being increased, they are as a rule notably diminished, only regaining the normal when the jaundice is passing off.

III. AUTHOR'S OBSERVATIONS.

It is on this point, as to the relation between the blood changes and the bile changes, that my observations yield information.

¹ Stadelmann, "Der Icterus und seine Verschiedene Formen," p. 247.

They relate to the action of toluylenediamin, and go to show that the concentration of bile, so marked a feature of its action, is due to an extensive catarrh of the bile ducts, extending from their origin downwards towards the duodenum, occasioned by the excretion of the poison or its derivatives through the bile.

It is the increase of the catarrhal viscid mucus thus occasioned that causes the concentration of the bile, and finally arrests for the time being its flow altogether.

Action of Toluylenediamin on Duodenum and Bile Ducts.

EXPERIMENTS.

EXPERIMENT 63.—SMALL DOG ; weight, 4400 grammes.

Nov. 24, 1887.—0·5 gramme toluylenediamin in neutral saline solution injected subcutaneously.

Nov. 26.—Jaundice of conjunctivæ well marked, also evident in skin of ears and mucous membrane of gums.

Nov. 28.—Weight 4300 ; jaundice very pronounced all over body, especially seen over abdomen.

Nov. 29.—Jaundice still pronounced ; weight, 4050. Animal killed with chloroform.

Liver.—Greatly jaundiced, large, soft, and somewhat fatty looking.

Gall bladder.—Contains a quantity of extremely dark, thick, inspissated bile.

Periphery of lobule presents a bright, golden-yellow appearance, seen on microscopic examination to be due to the presence of large masses of yellow material. Many of even the larger bile ducts plugged with inspissated bile.

Great stasis of bile also in bile capillaries in centre of lobule.

Intralobular blood capillaries filled with coloured remains of hæmoglobin and red corpuscles.

Stomach.—Firmly contracted ; empty ; mucous membrane thrown into rugæ, of a pale yellow colour.

Duodenum.—Appearances very striking. From the pylorus downwards, for a distance of about 12 inches, its mucous membrane is extremely swollen and congested, showing at parts small hæmorrhages. This is most marked at the upper part of the duodenum, especially around the opening of the common duct.

The congestion and swelling of mucous membrane diminish in intensity from this point downwards, and disappears altogether about the commencement of the jejunum.

On comparing with the mucous membrane from the duodenum of a healthy dog, the mucous membrane is seen to be soft and swollen, and on section twice to three times as thick. Small hæmorrhages are seen in its substance.

EXPERIMENT 64.—FOX-TERRIER DOG ; weight, 7·15 kilogs.

Dec. 2, 1887.—Spleen excised with full antiseptic precautions ; edges of abdominal incision brought together with catgut ; skin edges with silk.

Dec. 5.—Animal recovered ; weight, 6450 ; 0·5 gramme toluylenediamin injected subcutaneously.

Dec. 6.—Conjunctival jaundice.

Dec. 7.—Pronounced jaundice all over body.

Dec. 8.—Jaundice still more marked; weight, 6050.

Killed with chloroform.

Peritoneal wound healed.

No inflammation.

Liver.—Very dark and full of blood. Lobules not distinguishable to naked eye. Microscopically, the central part of each lobule presents the most beautiful natural injection of the bile capillaries with bile.

Gall bladder.—Contains a small quantity of intensely dark bile.

Stomach.—Mucous membrane normal, pyloric end bile-stained.

Duodenum.—Contains a large quantity of deeply bile-stained viscid mucus. The mucous membrane is greatly swollen, soft, and congested, with here and there punctiform hæmorrhages. The congestion is most intense at the upper part around the opening of the common bile duct, and diminishes gradually from there downwards, till at a distance of some 10–12 inches from the pylorus the mucous membrane assumes a normal healthy appearance. The intestinal mucous membrane throughout is covered with deeply bile-stained thick viscid mucus.

The appearances are similar in character to those presented in foregoing experiment, only less marked.

EXPERIMENT 121.—Nov. 27, 1889. SMALL DOG; weight, 4·75 kilogs.; 0·3 grammes toluylenediamin injected subcutaneously.

Nov. 26.—100 c.c. dark bilious-looking urine.

Nov. 27.—Weight, 4·5 kilogs.; well-marked jaundice; 160 c.c. urine, deeply bile stained.

Nov. 28.—Weight 4·35 kilogs.

Jaundice very pronounced.

Killed with chloroform.

Stomach.—Empty; mucous membrane thrown into folds, normal in colour and appearance; towards pyloric end slightly bile-stained.

Duodenum.—The mucous membrane of duodenum is congested and ecchymosed, presenting marked injection at parts. The congestion and ecchymosis commences on a level with the papilla on which the bile duct opens; and is very marked over a tract of 3 inches in extent from this papilla downwards.

Just below the papilla the congestion has a circular arrangement around a central deeper and paler part, the appearance at first glance resembling that of an ulcer. The floor, consisting of follicular tissue, is pale; around the margins the villi are swollen, congested, and ecchymosed. At the upper part three such congested follicular patches—axis transverse to that of gut—measuring 13 mm. by 4 mm., 10 mm. by 5 mm., the third incomplete. One inch lower down another similarly congested patch, 11 mm. by 4½ mm.; and 1½ inches still lower down, another, 11 mm. by 7 mm.

The congestion extends from here the whole way down to the ileo-cæcal valve, without, however, any ecchymoses; the mucous membrane swollen and cedematous. Just above the ileo-cæcal valve, over an area of 3½ inches in extent, there is a repetition of the redness, swelling, and ecchymosis seen at the upper part of the duodenum. Near lower end of ileum, follicular patches prominent and swollen, but not reddened. At this point a considerable quantity of dark brown bile, sufficient to fill the lumen of the gut; elsewhere throughout the gut, deeply bile-stained mucus.

The whole wall of the gut is affected by the swelling, most of all, however, the mucous membrane.

A number of measurements made on a healthy dog give an average thick-

ness of $2\frac{3}{4}$ mm. for wall of gut; the measurements here give a thickness of $4\frac{1}{4}$ –5 mm., the mucous membrane alone being $3\frac{3}{4}$ mm. thick.

EXPERIMENT 129.—Dec. 7, 1889. Dog; weight, 5·5 kilogs.; 0·25 gramme toluylenediamin injected subcutaneously.

- Dec.* 8.—80 c.c. clear straw-coloured urine.
No bile pigments.
Gives marked reaction of toluylenediamin.
- Dec.* 9.—Urine slightly darker in colour.
Still no bile pigments.
Reaction of toluylenediamin distinct but less marked.
- Dec.* 10.—Distinct reaction of bile pigments in urine.
No jaundice of skin or conjunctivæ.
- Dec.* 11.—*Urine*—Distinct reaction of bile pigments.
No reaction of toluylenediamin.
0·34 gramme toluylenediamin subcutaneously.
- Dec.* 17.—Weight, 4·55. No jaundice.
Killed with chloroform.

Duodenum and intestine.—On opening intestine from below upwards, mucous membrane is seen to be of pale colour and healthy appearance up to within 12–18 inches of pylorus. It then shows slight traces of congestion, but these are not marked, and are not such as would attract attention.

EXPERIMENT 133.—Dec. 10, 1889; weight, 10·9 kilogs.; 0·5 gramme toluylenediamin injected subcutaneously.

- Dec.* 14.—10·1 kilogs.
- Dec.* 15.—0·5 gramme injected.
- Dec.* 16.—9·25 kilogs.
- Dec.* 17.—8·95 kilogs.
Killed with chloroform.

Extreme jaundice from second day. During whole time the animal took no food and rapidly emaciated.

Stomach.—Empty. Mucous membrane thrown into folds, pale and normal.

Duodenum.—Even on opening abdomen, the duodenum seen to be affected, its walls turgid, swollen, and doughy to the touch. On being opened, the most intense inflammatory congestion of its coats, especially the mucous and submucous coats; the lumen of the gut narrowed, and filled with clear, thick mucus free from bile. The congestion and swelling has its greatest intensity around the opening of the common bile duct, from which thick mucus can be seen issuing; and for a distance of about 8 inches downwards from the point it is of the most intense character, the whole walls greatly œdematous and thickened.

Below this it gradually fades off, but throughout the whole of the small intestine the mucous membrane is considerably swollen and congested, the follicular patches here and there being very prominent by the congestion around their margins.

The appearances are accurately represented in the accompanying Plate, from a drawing made immediately on opening the duodenum (see Plate XVII.).

Summary of Foregoing.

In all these cases then, following the injection of toluylenediamin, there was found a condition of congestion and catarrh of the mucous

membrane of the duodenum, commencing on a level with the opening of the bile ducts, and always having its greatest intensity around these openings. The degree of congestion varied in different cases. In only one case was it of so slight a nature that it might, perhaps, have been overlooked, and that was the only case in which there was no jaundice. In all the other cases the condition of congestion was very marked. In the last, so great was the swelling of mucous and submucous coats, that the lumen of the duodenum was greatly lessened, the contents being clear, colourless, viscid mucus, free from bile.

In respect of its intensity, the condition in this last experiment was exceptionally striking. The attempt to produce it was purposely made. My object was not merely to produce extreme jaundice, but to see whether, by giving another large dose (0.5 gramme) while the jaundice was still very marked, the duodenal condition could be correspondingly intensified. The result was that all the essential features were intensified, especially the limitation of the congestion upwards, and its great intensity around the opening of the bile ducts. In addition, however, in this case, the catarrh of the bile ducts was very manifest—the clear viscid mucus projecting from the orifice of the common bile duct being of the same character as that occupying the duodenum itself.

As regards the relation of this duodenal condition to the jaundice, it will be noted that in only one case was there little or no obvious jaundice (although bile pigments were present in the urine); and that was the only case in which the duodenal condition was so slight that it might conceivably have been overlooked (Exp. 129). In the other cases the swelling and cedema of the mucous membrane was such that the effect of such a condition, if extending to the bile channels, could not but be obvious. The animals were all deeply jaundiced. A condition of catarrh falling far short of that here produced would amply suffice to retard, and, if continued, finally arrest the flow of bile along the bile channels.

The catarrhal condition was, however, not confined to the duodenum. From the swelling of the papilla on which the bile duct opened, and the presence in the orifice of the duct of colourless mucus similar to that lying within the duodenum; from the circumstance, further, that in all cases alike the congestion and swelling had a maximum intensity around the bile duct openings, it seemed that whatever had occasioned the condition had reached the duodenum through the bile.

To the duodenal condition *per se*, as a factor in producing the obstruction to the flow of bile by extension upwards of the catarrh into the common duct, I attach little or no importance. But as an indication and visible evidence of the degree of inflammatory catarrh that can be set up in a mucous surface by the action of an irritant, I attach to it special importance.

It is to be noted that the drug was not administered by the mouth, but hypodermically; that the mucous membrane of the stomach above

the pylorus was always free from the slightest trace of abnormality or congestion; and that precisely on a level with the opening of the bile duct the mucous membrane of the duodenum had undergone this extensive swelling, œdema, and congestion. The irritant—using that term in its widest sense—appeared to have reached the duodenum through the bile; and its action on the mucous membrane of the bile duct, judging from the similarity in character of the colourless mucus issuing from the bile duct, had been the same as on the mucous membrane of the duodenum.

IV. EXCRETION OF TOLUYLENEDIAMIN THROUGH THE BILE.

I made the following experiments to ascertain whether the poison was excreted through the liver, and could be found in the bile:—

EXPERIMENT 119.—Nov. 19, 1889. Dog; weight, 10·15 kilogs.

Narcotised with morphia (0·15 gramme).

Small dose of curare given.

Right ureter exposed, and a cannula introduced.

Common bile duct exposed, and a glass cannula introduced.

Gall bladder found distended with richly-coloured *bile* (bilirubin colour).

11.45 A.M.—Operation completed.

12 noon.—Bile flowing fairly well; some hindrance to flow of urine.

12.7 „ —Still no flow of urine; 20 c.c. warm normal saline solution injected into vein.

1 P.M.—3·5 c.c. of urine }
3 c.c. of bile } = Sample A.

10 c.c. blood withdrawn from femoral artery = I.

1.30 „ —1·6 c.c. urine }
2·3 c.c. bile } = Sample B.

1.35 „ —0·5 gramme toluylenediamin in 20 c.c. normal saline injected into jugular vein.

2 „ —Secretion of urine has been very slow.

1·9 c.c. urine }
2·2 c.c. bile } = Sample C.

2.33 „ —2 c.c. bile = Sample D.

3 „ —1·4 c.c. bile = Sample E.

2·2 c.c. urine = Sample D. and E.

The latter muddier and distinctly darker in colour than first specimen.

5 c.c. of blood withdrawn into saline solution = Sample II.

3.30 „ —2 c.c. bile = Sample F.

Bile secretion during last half-hour has been greater in quantity; colour of bile is less than in Sample E.

No flow of urine.

3.55 „ —20 c.c. of $\frac{3}{4}$ per cent. NaCl solution injected into vein.

3.56 „ —Urine again flowing.

4 „ —1·1 c.c. bile = Sample G.

0·6 c.c. urine.

4.35 „ —5 c.c. blood withdrawn = III.

5.30 „ —2·7 c.c. bile.

1·4 c.c. urine.

5.35 P.M.—5 c.c. blood withdrawn = IV.

5.45 „ —4 c.c. bile = Sample H.

1.4 c.c. urine = Sample H.

Urine from bladder obtained by squeezing.

Experiment stopped.

Animal killed by bleeding from femoral artery.

Blood of a dark chocolate colour.

I. Greater portion withdrawn into a beaker containing $\frac{3}{4}$ per cent. NaCl solution.

II. Remainder into 8 per cent. NaCl solution.

Placed below in cold cellar.

Weather at the time cold.

Nov. 20, 10 A.M.—I. Has firmly coagulated. A large quantity of serum expressed.

A portion of this serum carefully drawn off with a pipette. No trace of blood-colouring matter either to naked eye or on spectroscopic examination. No hæmoglobin.

II. Supernatant serum quite colourless. No trace of hæmoglobin on spectroscopic examination.

Examination of Bile for Toluylenediamin.

Method.—The method I employed was a colorimetric one, first suggested to me by the phenylenediamin test for nitrites in water. I found that the process could be reversed. Toluylenediamin, even in extremely dilute solution, gives a very well-marked reddish-brown colour reaction on adding to the solution a drop of dilute hydrochloric acid, and subsequently a drop or two of a solution of nitrite of sodium.

I had at first some difficulty in applying the test in the case of coloured fluids, like bile, urine, blood.

After a number of experiments, with the object of decolorisation, *e.g.* with charcoal, heating, etc., the best method, I found, was to dilute the urine and bile greatly, and to use as the comparison solution one of normal bile and urine diluted to the same colour. Thus, in the case of bile, the method was as follows:—

1. A few drops of the bile placed in a test tube and diluted up to a certain point.

2. In another test tube a small quantity of normal bile diluted till the colour was the same as in 1.

On applying the test to the latter the yellow colour entirely disappeared and solution remained colourless.

If toluylenediamin were present, even in minute trace, a faint brownish coloration was seen on looking through a deep layer of the fluid; and this became quite marked when more was present.

The solutions were placed in cylindrical, flat-bottomed glasses of uniform diameter, and the degree of coloration was judged by looking down through the fluids against a background of white paper on which the glasses stood.

In the foregoing experiment the results, as regards the bile, were as follows:—

Samples A. and B.—Taken before the injection of toluylenediamin. No reaction.

Sample C.—Twenty-five minutes after the injection. No reaction.

„ D.—One hour after injection. Merest trace of characteristic colour reaction.

„ E.—One and a half hours. Still very faint, but more marked than before.

„ F.—Two hours. Reaction easily appreciable; even in thin layers.

„ G.—Two and a half hours. Still more marked.

„ H.—Four hours. Diluted up to 28 c.c. Of this, 2½ c.c. taken and diluted, and tested. Its yellow colour gives place to a distinct brownish colour. A control solution of normal dogs' bile similarly diluted and tested, yellow colour completely disappears. No trace of reaction in this latter.

Quantitative Estimation of Toluylenediamin in Bile.

The method I employed was to ascertain what quantity of a standard solution of toluylenediamin was necessary when added to normal bile to produce the same degree of colour reaction as the bile under examination.

The following was the standard solution:—

Either 0·3 mgrm. of toluylenediamin in 100 c.c. water, or 1 mgrm. in 100 c.c.

The last specimen of bile—4 hours after injection—gave a colour reaction equivalent to 0·47 mgrm. of toluylenediamin.

Examination of Blood withdrawn during Experiment.

1. Withdrawn before the injection.

Gives no reaction of toluylenediamin.

2. Three hours after injection.

Gives a trace of reaction.

Examination of Blood after Death.

PORTION I.—Withdrawn into $\frac{3}{4}$ per cent. NaCl solution.

Both serum and clot give distinct reaction of toluylenediamin.

The method employed was as follows:—

Clot beaten up in water, raised to boiling point, and filtered. The filtrate treated with equal parts of methylated spirit, and again filtered.

A colourless solution then obtained.

Serum raised to boiling point and filtered.¹

Treated in this way—the serum contained an estimated quantity of 0·6 mgrm.

Serum.—Total quantity, 60 c.c.

2 c.c. gave distinct colour reaction, equivalent to colour reaction in water of 0·02 mgrm.

60 c.c. = 0·6 mgrm.

Clot.—Total quantity of fluid, 70 c.c.

2 c.c. = Distinct reaction.

70 c.c. = 0·7 mgrm.

Total quantity of toluylenediamin in blood, 1·3 mgrms.

¹ I subsequently found it better not to heat the serum, but to test it pure, using healthy serum as the control solution.

Examination of Urine.

SAMPLES D and E.—(2·2 c.c.) One and a half hours after injection. Distinct reaction of toluylenediamin.

Diluted to 30 c.c.

2 c.c. contains 0·05 mgrm.

30 c.c. „ 0·75 „

SAMPLE H.—(1·4 c.c.) Four hours after injection.

Diluted to 60 c.c.

2 c.c. requires 7 c.c. of standard solution.

(1 mgrm. in 100 c.c.) of toluylenediamin = 0·07 mgrm.

60 c.c. = 2·10 mgrm.

Urine of bladder diluted up to 50 c.c.

2 c.c. required 1·3 c.c. of standard solution = 0·13 mgrm.

50 c.c. = 3·25 mgrms.

Total found in urine = 6·10 mgrms., giving an excretion of 2·85 mgrms. from left kidney, and 3·25 mgrms. from right kidney.

In this experiment there was definite evidence of an excretion of the poison through the bile as early as one hour after its injection, and by the fourth it was in appreciable quantity (0·47 mgrm.).

At the same time it was being excreted in the urine—the total quantity excreted in 4 hours being 6·10 mgrms.

V. EXCRETION OF TOLUYLENEDIAMIN THROUGH THE URINE.

EXPERIMENT 121.—Dog; 4·75 kilograms. in weight.

Nov. 25.—0·3 gramme toluylenediamin subcutaneously.

Nov. 26.—100 c.c. dark bilious urine.

Whole carefully collected, amounting with washings to 150 c.c.

3 c.c. when diluted gave colour reaction equal to 3·4 c.c. of standard solution of toluylenediamin. (10 mgrms. in 100 c.c.)

3 c.c. = 0·34 mgrm.

150 c.c. = 17 mgrms. (0·017 gramme).

Nov. 27.—Urine dark bilious. With washings, 230 c.c.

No trace of toluylenediamin in reaction.

Only one-eighteenth part of the amount injected accounted for in the urine; the remainder broken up within the body.

EXPERIMENT 125.—Dog.

Dec. 2.—0·4 gramme injected.

Killed by bleeding 1½ hours later; the blood withdrawn into 200 c.c. $\frac{3}{4}$ per cent. NaCl solution.

Blood.—Twenty-four hours later firmly coagulated; the serum colourless, showing no trace of hæmoglobin bands.

Both serum and clot (the latter after being treated with distilled water and boiled) gave a slight reaction of toluylenediamin; the total being estimated as not more than 1 mgrm.

Duodenum.—Mucous membrane covered with thick dark bile for a distance of 6 inches, and slightly congested. Mucus and bile scraped off, diluted with water, heated, and filtered. Filtrate gave faintest reaction.

The following experiments show the delicacy of the test employed:—

EXPERIMENT 131.—RABBIT bled into 50 c.c. $\frac{3}{4}$ per cent. NaCl solution, to which 10 mgrms. of toluylenediamin had been added.

Serum pipetted off; quantity, 100 c.c.

2 c.c. gave colour reaction equivalent to 0.19 mgrm.

100 c.c. = 9.5 mgrms.

Blood clot gave no reaction.

Total accounted for, 9.5 mgrms = (95 per cent.).

EXPERIMENT 132.—RABBIT bled into 50 c.c., 10 per cent. NaCl solution, to which 10 mgrms. of toluylenediamin had been added.

Serum carefully pipetted off; gives marked reaction of toluylenediamin.

Total quantity, 100 c.c.

2 c.c. gave colour reaction equal to 0.195 mgrm.

100 c.c. gave colour reaction equal to 9.75 mgrms.

Total accounted for 9.75 out of 10 mgrms. injected = 97.5 per cent.

VI. SUMMARY OF FOREGOING.

The foregoing experiments may be regarded as definitely establishing that the bile is one of the channels through which toluylenediamin is excreted from the body.

As early as 1 hour after injection traces of it could be detected in the bile (Exp. 119 and Exp. 125); and by the fourth hour it was present in an appreciable, albeit still very small, amount.

In the present relation, however, the actual amount excreted is a matter of comparatively little importance. The point of importance, as it appears to me, is that it is excreted at all through this channel.

The other experiments I have recorded show that toluylenediamin is broken up very soon after its introduction into the body; and that the greater part of it is either destroyed, or leaves the body in some other form. Information on this point is afforded most clearly by Experiment 121, in which of the amount of toluylenediamin injected (0.3 gramme), only about $\frac{1}{8}$ th part could be discovered in the urine (0.17 gramme).

No less striking in the same relation is the small amount of the poison to be detected in the blood even 1 hour after its injection. Thus $1\frac{1}{4}$ hours after injection of 0.4 gramme (Exp. 125), only a trace could be found in the whole quantity of blood.

It may be, of course, that the poison has already entered into some combination, *e.g.* with hæmoglobin, which prevents its presence being detectable. It certainly is not present in free form; for the Experiments 131 and 132 show that the method employed for detecting it is sufficiently delicate to recognise 95 to 97 per cent. of the substance when added to blood outside the body.

Considering, then, the small amount present at any time in the

blood, and the small proportion ($\frac{1}{8}$) that succeeds in escaping unbroken from the body, the trace found in the bile is not inconsiderable.

The question then arises, Are the catarrh and congestion set up in the bile ducts and duodenum, after the injection of toluylenediamin, to be ascribed to the irritant action of this small trace of poison in the bile?

I think this extremely improbable, and for this reason. Toluylenediamin has a slight irritant action, especially in its stronger solution ($2\frac{1}{2}$ or 5 per cent.) when injected subcutaneously, causing some inflammation, with subsequent necrosis of overlying skin and scab formation.

Such an action, however, is, I consider, no criterion of what its action on the mucous surfaces of the bile ducts or duodenum may be. I think it extremely improbable that in the small amount in which it is present in the bile, it can exert such an irritant action as that I have described.

It is, I conceive, much more likely that the irritant action of the bile after toluylenediamin poisoning is due to the presence of derivatives of the poison, and not to the poison itself. The foregoing observations show that only a small proportion ($\frac{1}{8}$, Exp. 121) passes through the body unchanged. The remainder is either destroyed, or converted into derivatives, which, like the poison itself, are in all probability excreted through the urine and the bile.

One reason that inclines me to believe that it is to the products, rather than to the poison itself, that the irritant action is to be ascribed, is the following.

I have not found any trace of duodenal catarrh in rabbits and cats after administration of toluylenediamin. And yet any irritant action it possesses on subcutaneous injection is as marked, according to my experiments, in rabbits as in dogs.

Why, then, does the effect of its action on the duodenum differ in the two cases? It is, I think, more likely that this difference is due to a difference of metabolism. Toluylenediamin is much better borne by rabbits than by dogs.

The important point is, that, *whatever the nature of the irritant*, these observations show that *it is contained in the excreted bile*; that *it reaches the duodenum through the bile*, and that *it must be of powerful nature to induce such an inflammatory congestion as that described*.

Cause of the Jaundice.

The explanation of the jaundice produced by toluylenediamin appears to me, then, to be—that products of the poison are excreted through the bile, and excite swelling and catarrh, with increased secretion of mucus, in its course down the bile passages into the duodenum.

The involvement of the duodenum I do not consider at all necessary

for the production of the jaundice. It is a mere adjunct to the catarrh of the bile ducts. It is only in exceptionally severe cases that it occurs. The primary condition in causing the obstruction is, I consider, the catarrh of the bile ducts at their origin. Under the low pressure at which the bile is excreted, a slight degree of catarrh in this situation suffices to cause, first, a retardation in the flow and increased consistence of the bile (end of first stage), and as the catarrh spreads down the bile ducts, it finally arrests its flow altogether (second stage).

This view, as to the relation of the catarrh to jaundice, differs essentially, I would point out, from the one usually accepted,¹ according to which the catarrh spreads upwards from the duodenum. The latter must always be preceded by duodenal catarrh. In the present case, as I have said, I consider the duodenal condition quite unnecessary to the production of the catarrh. For the course of the catarrh is from above downwards; it commences in the bile radicles, and extends downwards; and in many cases it may not even reach the duodenum. As it is produced by substances excreted by the liver, it involves, therefore, the whole bile radicles and smaller ducts simultaneously, and to a like degree. In slight cases it may not extend beyond these; and it would be quite impossible (apart from its result, jaundice) to recognise it after death.

As a factor in causing jaundice, it derives its chief importance from the widespread character of the obstruction it produces, rather than from its high degree. The increased secretion of mucus occasions increased viscosity of bile sufficient to occasion a certain amount of obstruction and a certain degree of jaundice.

VII. COMPARISON OF FOREGOING WITH STADELMANN'S RESULTS.

Stadelmann² was never able to observe any obstruction to the free exit of bile into the duodenum. And if there could be any doubt on this point, he regarded his experiments on dogs with biliary fistulæ as conclusive.

"If jaundice could be equally well produced in them, the jaundice could not be catarrhal—the result of catarrh or inflammation of the duodenum extending up into the ductus choledochus."

I have analysed Stadelmann's original experiments on which he bases the above conclusions, and I here present the result.

His first two experiments are of no value in the present relation, as the animals were not killed.

EXPERIMENT 3.—LARGE DOG; 20 kilogs. in weight; 0·4 gramme hypodermically.

Next day.—No jaundice; 0·4 gramme more.

Following morning killed; indistinct icterus of conjunctiva.

¹ Murchison, "Diseases of the Liver," 3rd edition, 1885, p. 159.

² *Loc. cit.*, p. 120.

Sectio.—Liver somewhat icteric, but by no means so markedly as in other cases. Bile ducts, gall bladder, common bile duct, full of bile and considerably distended. Common duct opens free into duodenum, and “on gentle pressure” bile can be squeezed out of it.

Small bile ducts extraordinarily full of bile. Contents of intestine much bile-stained.

EXPERIMENT 4.—20 kilogs.; 1·0 gramme hypodermically; found dead and cold next morning.

Ductus choledochus free.

No injection of intestine.

Liver only in parts icteric; gall bladder full, and also bile ducts. On cut surface of liver “bile flows freely out of bile ducts.”

Intestinal contents strongly bile-stained.

EXPERIMENT 5.—5 kilogs.; 0·5 gramme hypodermically; next morning found dead, although still warm.

No jaundice of conjunctivæ or mucous membrane.

Result same as in foregoing.

EXPERIMENT 6.—MIDDLE-SIZED DOG; 0·3 gramme hypodermically; hæmoglobin in urine.

No jaundice over 7 days later.

0·2 into jugular vein.

Two days later no jaundice.

Then 0·3 into vein of foot.

Next day.—Urine jaundiced, but no blood; dog no longer observed.

EXPERIMENT 7.—5 kilogs.; biliary fistula without ligaturing common duct.

Eight days later 0·2 *per os*.

Two days later well-marked jaundice, which increased from day to day.

(How long after not stated) Dog killed.

“No sign of catarrh” in intestine.

Intestinal contents strongly bile-stained.

Common bile duct pervious to a probe.

“On pressure over the upper part of it,” bile flowed into intestine.

No mucous plug anywhere discoverable in bile ducts.

EXPERIMENT 8.—SMALL DOG; 0·15 gramme by mouth.

Two days later marked jaundice.

Two days later, *i.e.* on fourth day, found dead.

Sectio.—No signs of catarrh of mucous membrane of intestine; large quantity of bile in intestine; gall bladder quite full; bile ducts also full; “on gentle pressure” over the gall bladder, bile flows into intestine.

EXPERIMENT 9.—0·25 gramme hypodermically; slight jaundice, which gradually faded away from fourth day onwards.

At end of 8 days experiment broken off.

Four days later 0·3 gramme hypodermically.

Two days later another 0·3 gramme.

Three days later—so ill that it can hardly stand; killed.

Sectio.—Moderate icterus; gall bladder filled with green bile, whose exit into intestine is free; no signs of a catarrh of intestine; contents of intestine green-coloured.

Out of these nine experiments, three are valueless for our present purpose, as the animals were not killed (Exp. 1, 2, 6).

On comparing the remaining six with those recorded by myself, one difference is noticeable, sufficient of itself to account in no fewer than three cases for the absence of any duodenal condition comparable to that I have described. This difference is that in my experiments the animals, with one single exception, were always killed when the jaundice was at its greatest height; while in the foregoing experiments of Stadelmann the animals in two cases (Exp. 4, 5) died within 24 hours of acute poisoning, before any jaundice had developed; and in a third (Exp. 3), there was only a doubtful jaundice of conjunctiva at the time of death.

That, under these circumstances, no pronounced changes were found in bile ducts or duodenum, need not surprise, since as a matter of fact there was no complete obstruction.

Nevertheless there was, I consider, in all three cases evidence of commencing obstruction along the course of the bile ducts. For in all there was great stagnation of bile in the bile ducts, especially the smaller, notwithstanding the fact that the common duct opened free into the duodenum. There was clearly, therefore, no obstruction in the duodenum or at the mouth of the duct; and if, as Stadelmann thought, catarrh could only originate in the duodenum, and spread upwards into the bile ducts, the jaundice could not be catarrhal.

But the experiments do not justify the conclusion that there was no obstruction to the passage of bile into the duodenum, and no catarrh of the bile ducts. Obstruction, I think, there evidently was all along the bile ducts, since, notwithstanding that they were distended, and that the opening of the bile duct into the duodenum was free, "gentle pressure" was in all cases necessary to make the bile flow into the duodenum.

In the remaining three experiments there was a similar absence of any duodenal condition. "On pressure" bile could always be made to pass into the duodenum; or a probe could be passed through the common bile duct (Exp. 7). It would, I think, be fallacious, however, to regard this as proof of the absence of any obstruction of catarrhal nature.

With regard to this last test, I do not doubt that in the worst case of duodenal inflammation and catarrh among my experiments, I should have been able to pass a probe through the bile duct had I attempted it. For, after all, the obstruction is only caused by thick viscid mucus, and catarrhal swelling of the epithelium of the bile ducts, and that is not in itself sufficient to resist a probe, however effective it may be in stopping the flow of bile.

The further point to which Stadelmann attaches importance in favour

of the non-catarrhal origin of the jaundice is: the occurrence of jaundice "equally well" in dogs with biliary fistulæ—in whom, therefore, the bile flows freely through a fistula in the gall bladder, and its flow is independent of any condition of the duodenum or the common bile duct (Exp. 7).

On this I need hardly dwell, since I have shown that the catarrh of the bile ducts produced by this substance is altogether independent of the duodenum, and spreads downwards, not upwards. Such a catarrh is not likely to be affected by the presence of a biliary fistula, except in so far as the common bile duct is thereby cut off, and the length of the biliary tract likely to be affected by it correspondingly shortened.

As a matter of fact, Stadelmann's experiments clearly show that jaundice is not "equally well" produced in dogs with biliary fistulæ as in normal dogs. On the contrary, as he himself admits, larger doses were always required in the former than in the latter to produce a similar degree of jaundice, precisely as one might expect from a shortening of the length of duct affected by the catarrh.

The foregoing observations and conclusions relate, in their entirety, to the jaundice of toluylenediamin poisoning.

They show that in catarrh set up by the irritant action of the poison on the mucous lining of the bile ducts from their origin downwards, we have an efficient cause for the increased viscosity of bile and obstruction to its flow.

As we have seen, the two special factors in bringing about the increased viscosity of bile are, according to Stadelmann (1) the increased formation of bile pigments (polychromia), and (2) the specific action of the poison on the liver cell.

VIII. RELATION OF JAUNDICE TO HÆMOGLOBINÆMIA.

It is necessary to consider what is the influence of an increased formation of bile pigments (polychromia) *per se*, on the consistence of the bile, and through the latter on jaundice.

That some relation exists between these two conditions is evident from the frequency with which some degree of jaundice is met with, both clinically and experimentally in cases where hæmoglobin has been set free in the blood and passes into the urine.

The observation that some relation exists between the two conditions formed in Kühne's hands the very starting-point of the doctrine of a hæmatogenous jaundice independent of any obstruction.

Kühne¹ considered this relation an absolute and quantitative one. An excess of free hæmoglobin in the blood was of itself sufficient, according to him, to occasion a certain degree of jaundice—such a degree at least as to cause bile pigments to appear in the urine.

¹ "Lehrbuch der physiol. Chemie," 1868.

The later experiments of Tarchanoff and Stadelmann seemed to lend additional support to this view.

Thus, according to Tarchanoff,¹ bile pigment is found regularly in the urine of dogs after injection of water or hæmoglobin into the blood.

And, as we have seen, Stadelmann attaches quite a special importance to the increase of bile pigments (polychromia) which occurs under such circumstances, as one of the chief factors in occasioning a form of jaundice. After injection of large quantities of hæmoglobin, he usually found a trace of bile pigment in the urine some time or other in the course of the experiment.

Stadelmann's observations go still further; for they show in what manner an excess of free hæmoglobin may produce jaundice. The injection of free hæmoglobin into the blood, or its liberation within the circulation by use of distilled water, is followed by changes in the bile, namely, increase of bile pigments, increased viscosity of the bile, diminution of bile acids—changes, therefore, similar in character to those caused by toluylenediamin or arseniuretted hydrogen. And the explanation of the jaundice that may occur under such circumstances is, according to him, the same, namely, obstruction caused by the high concentration of the bile, which is, in turn, related to the polychromia. Nothing at first sight seems wanting, therefore, to an understanding of the relation between hæmoglobinæmia and jaundice.

And yet other data, to which I must now direct attention, appear to me to indicate that the relation is by no means so simple and so constant as the above would appear to show. *They justify rather the conclusion that hæmoglobinæmia per se, apart from the operation of other factors, is not sufficient to cause jaundice.*

Here, however, I must guard myself against a possible misconception. I am not here disputing that there is the closest relation between certain forms of jaundice and increased destruction of blood (including, in some cases, hæmoglobinæmia). On this point both clinical and experimental observations are at one; and the subject is one to which I shall have presently to refer. What I am here endeavouring to ascertain is the influence of a simple excess of free hæmoglobin in the blood in producing jaundice, apart from all other possible factors.

Hæmoglobinæmia is not of itself sufficient to cause bile pigments to appear in the urine or jaundice.

And, first of all, I would direct attention to observations throwing doubt on the accuracy of the statement that excess of free hæmoglobin in the blood is sufficient of itself to cause bile pigments to appear in the urine.

Results in support of such a view have only been obtained in one class of animals (dogs), and even in them not constantly; whereas in rabbits the balance of experimental evidence from all sides is, I consider, decidedly against the view that hæmoglobinæmia *per se* is sufficient to cause jaundice.

¹ *Arch. f. d. ges. Physiol.*, Bonn, bd. ix.

Dogs.—As regards dogs, the significance to be attached to bile pigments in the urine is a little complicated by the circumstance, noted by many others, which I can fully confirm, that it is not uncommon to find a trace of bile pigments in the urine of apparently healthy dogs. Unless this source of fallacy be kept in mind, and care be taken by suitable precautions to avoid it, erroneous conclusions may be drawn. In my experience, this is specially likely to be the case in old dogs. To avoid this source of fallacy it is, I think, necessary to employ only young healthy dogs, whose intestinal canal has been well cleared out by castor oil or calomel; the animals being kept on a milk-and-bread diet for some days previous to experiment. This tendency to the occurrence of a slight degree of icterus in dogs is connected, in my opinion, with their habit of eating garbage and refuse of various kinds. It is not uncommon to find in such animals some degree of catarrh of the mucous membrane of the small intestine.

The experiments of Naunyn¹ conclusively show that if care be taken to avoid the above source of fallacy, hæmoglobinæmia even in dogs does not necessarily cause bile pigments to appear in the urine. In only two out of six cases in which he caused hæmoglobinuria by injecting hæmoglobin subcutaneously, did the urine give any reaction to Gmelin's test for bile pigments; and in both of these cases the urine had given a slight reaction before the experiment. In the other four cases he failed to find any bile pigment in the urine, although there was marked hæmoglobinuria (and necessarily hæmoglobinæmia).

And although Stadelmann usually found a trace of bile pigment in the urine after injection of large quantities of hæmoglobin, there are, as it appears to me, certain features in his results which indicate that the presence of bile pigment was to be referred to other factors than the simple hæmoglobinæmia. Thus the quantity was at most a trace, and in no way proportionate either to the amount of hæmoglobin set free or to the resulting increase of bile pigments. This is not what one would naturally expect, if the presence of bile pigment in the urine be directly related to the hæmoglobinæmia, as Kühne supposed, or to the resulting increased formation of bile pigments (polychromia), as Stadelmann would have us believe.

Thus in one experiment (a) of the latter, where there was an increase of 80 per cent. in the bilirubin secreted, along with hæmoglobinuria, only a trace of bile pigment was found in the urine. While in another (Exp. 3), where the increase in bilirubin was less than 50 per cent., without hæmoglobinuria, there was a considerable quantity of bile pigment in the urine.

I have summarised the results of his experiments² in the following tables, for the purpose of bringing out the foregoing points. It will be seen from them that the one condition to which the jaundice is con-

¹ "Beiträge zur Lehre vom Icterus," *Arch. f. Anat. u. Physiol.*, 1868, p. 401.

² *Op cit.*, p. 23 et seq.

stantly related, is the degree of viscosity of the bile, not the degree of polychromia or hæmoglobinæmia.

EXPERIMENT (a).—Dog; 20 grammes of hæmoglobin injected in six portions between 10 A.M. and 8 P.M.

First period of 12 hours—

Bilirubin increased by 80 per cent.

Hæmoglobin, but no bile pigment in urine.

Second period of 12 hours—

Bile very dark. Viscid, diminished in quantity.

No hæmoglobinuria, but a trace of bile pigment in urine.

Third period—

Bile increased in quantity.

No trace of bile pigment in urine.

Bile acids considerably diminished at the very time the bilirubin most increased.

EXPERIMENT 1.—10·02 grammes hæmoglobin injected subcutaneously.

First period of 24 hours—

Bilirubin increased by 56 per cent.

Bile reduced to one-third normal quantity, dark, viscid.

No bile pigment in urine.

Second period—

Bile very dark and thick.

Trace of bile pigment in urine.

Third period—

Bile normal in consistence.

No trace of bile pigments in urine.

Bile acids.—First 12 hours. Unaffected.

Second „ Diminished by 36·8 per cent.

Third „ „ „ 44·5 „

EXPERIMENT 2.—10·82 grammes hæmoglobin subcutaneously injected.

First period of 12 hours—

Bilirubin increased by 11·96 per cent.

Urine normal.

Second period—

Bilirubin increased by 61 per cent.

Bile thick.

Urine normal.

Third period—

Bilirubin increased by 35·8 per cent.

Bile of normal consistence.

Urine normal.

Quantity of bile fairly normal throughout.

Bile acids showed no change.

EXPERIMENT 3.—13·94 grammes hæmoglobin injected into peritoneum.

First period of 12 hours—

Bilirubin increased by 12·3 per cent.

Bile very thick; quantity diminished.

No bile pigments in urine.

Second period—

Bilirubin increased 49·5 per cent.
 Bile thick; quantity diminished.
 Considerable quantity of bile pigment in urine.

Third period—

Bilirubin increased by 12·4 per cent.
 Bile normal in quantity and consistence.

Bile acids. First and second periods—

Diminished by about 17 per cent.
 Third period—slightly increased.

The relation, then, between hæmoglobinæmia or polychromia and jaundice is no mere quantitative one even in dogs.

And if this be true of hæmoglobinæmia, produced by injection of hæmoglobin or of distilled water, it is still more true of hæmoglobinæmia induced by poisons.

Thus in one of the foregoing experiments of Stadelmann (Exp. 6), there was hæmoglobinuria after injection of 0·3 gramme toluylenediamin without any jaundice supervening; and 9 days later, after a similar dose, there was jaundice without, however, any hæmoglobinuria.

Rabbits.—While then, as regards dogs, the evidence either way is inconclusive,—hæmoglobinæmia sometimes causing jaundice, sometimes not,—in rabbits there is no such uncertainty. The great preponderance of evidence is, I consider, decidedly against the view that hæmoglobinæmia *per se* suffices to cause jaundice, even in the slight degree necessary to cause bile pigments to appear in the urine.

Naunyn always failed to find bile pigments in the urine of rabbits after causing hæmoglobinuria.

Since then the list of those who have similarly failed includes the names of:—

Wickham Legg,¹ after the injection of bile acids.

Lauder Brunton,² after the injection of bile acids into the circulation, or of ether or dissolved blood corpuscles into the intestine.

L. Steiner,³ after the injection of water into the circulation of rabbits.

On this latter point my observations are in entire agreement with those of Naunyn and Steiner. Both after a slight and marked degree of hæmoglobinæmia, I failed to find bile pigments in the urine.

I append two experiments in point.

EXPERIMENTS 44 (Sept. 30, 1887).—RABBIT; 30 c.c. of distilled water injected into jugular vein.

Slight hæmoglobinuria, with yellow granular *débris* of hæmoglobin, passing off in 5 hours.

No bile pigments detectable in urine with Gmelin's test.

¹ "Bile, Jaundice, and Bilious Diseases," 1880, p. 235.

² "Handbook for Physiological Laboratory," 1873, p. 499.

³ "Ueber die hæmatog. Bildung des Gallenfarbstoffes," *Arch. f. Anat. u. Physiol.*, 1873.

EXPERIMENT 48 (Oct. 10, 1887).—RABBIT; 70 c.c. distilled water injected into jugular vein.

Marked hæmoglobinuria; urine contained yellow granular débris of hæmoglobin in large quantity; also hæmoglobin casts; well-marked guaiacum reaction. *No bile pigments.*

In some cases the results have varied in the hands of the same observer. Thus Graham Brown,¹ after subcutaneous injection of bile acids in rabbits, failed in most cases to find bile pigments in the urine, while in a few cases he succeeded.

Naunyn, who failed to discover bile pigments in the urine when he injected hæmoglobin into the circulation, found it after injecting thawed blood into the intestine;² an observation which Lauder Brunton³ failed to confirm.

These varying results may perhaps be partly explained either on the ground that the animals used were not in all cases the same, or that the conditions of the experiments were not in all cases alike—different agents being used to produce the hæmoglobinuria, and different methods of administration employed. Hitherto, on the view that the positive result was the common and natural one, the chief endeavour on the part of observers has been to explain the negative results. But as I have shown, even in dogs the result is not always positive; and when it is, it is not directly related to the quantity of hæmoglobin set free, or the resulting formation of bile pigment. In rabbits, however, a positive result is decidedly the exception. The position of matters is thus, I consider, reversed. So long as it was held that free hæmoglobin could become transformed into bile pigment within the blood, it was natural to expect that hæmoglobinæmia should cause bile pigments to appear in the urine; and no less natural, therefore, to regard as exceptional all cases where this did not occur. Now, however, that it has been shown by preponderance of evidence that the jaundice of blood disorder is not hæmatogenous, but hepatogenous (Stadelmann), the position of matters is, as I have said, reversed. If under the old (hæmatogenous) view the difficulty was to explain why hæmoglobinæmia should not always occasion some degree of jaundice, with our present knowledge the difficulty appears to me of another nature—to explain, namely, in what way hæmoglobinæmia, with its resulting polychromia, should cause increased viscosity of the bile and temporary arrest of its flow.

For the reasons I have adduced then, I consider that mere excess of hæmoglobin in the blood, or increase of bile pigments, however great, is not the sole factor determining these changes in the bile, with the resulting jaundice.

Jaundice may be of the most intense character, with only a comparatively slight polychromia (one-half increase in toluylenediamin

¹ *Proc. Roy. Soc. Edin.*, 1875, p. 528.

² *Op. cit.*

³ *Op. cit.* p. 499.

poisoning), or it may be slight or absent, with a threefold or fourfold increase (arsenious acid poisoning).

IX. RELATION OF BLOOD DESTRUCTION TO JAUNDICE.

What then is the relation between increased destruction of blood and jaundice? As I have shown in the foregoing section, it is, in my view, no mere *quantitative* one. Simple excess of free hæmoglobin in the blood, even when in quantity sufficient to cause hæmoglobinuria, does not necessarily of itself suffice to cause jaundice.

That jaundice, however, frequently occurs in conditions attended by increased destruction of blood is a fact about which there can be no dispute. The relation between the two conditions must thus be a *qualitative* one, but of what nature is by no means clear. Thus, in one class of animals (dogs), toluylenediamin causes jaundice without hæmoglobinuria; in another (cats), it causes hæmoglobinuria without jaundice; while in a third (rabbits), it causes apparently neither hæmoglobinuria nor jaundice. And yet in all three classes it occasions a destruction of blood. Moreover, even in the same animal its action sometimes varies. Thus in the dog it may occasionally cause hæmoglobinuria without jaundice (Stadelmann).

Various explanations of these differences have been put forward. According to Afanassiew,¹ the occurrence of jaundice alone, or hæmoglobinuria alone, or both together, depends on the *extent* of the preceding blood destruction, and on its *nature*.

He distinguishes three kinds of action of hæmolytic substances on the blood. The first is represented by the action of glycerine, which dissolves the hæmoglobin out of the corpuscles, leaving hardly any morphological remains of the latter within the blood. The free hæmoglobin escapes mostly through the kidneys, only a small portion being dealt with elsewhere (liver, spleen, or bone marrow).

The second kind of action is represented by that of toluylenediamin. This acts quite differently. It breaks the red corpuscles into pieces. These circulate in the blood, and accumulate in the liver, spleen, and bone marrow, where they are disposed of, only a part escaping through the kidney. When the dose is small, no hæmoglobin passes into the plasma. Hence, in slight cases, only jaundice occurs, produced by the increased excretion of bile; there is no hæmoglobinuria.

When the dose is larger, the remains of the red corpuscles are not sufficiently rapidly disposed of; they circulate in the blood, some of their hæmoglobin escapes into the plasma, and not only jaundice, but also hæmoglobinuria occurs.

The third kind of action is represented by that of pyrogallie acid.

¹ " Ueber die pathologischen anatomischen Veränderungen in den Nieren und in der Leber bei einigen mit Hämoglobinurie oder Icterus verbundenen Vergiftungen," *Virchow's Archiv*, 1884, *bd.* xlviii. s. 465.

It is intermediate in character betwixt the two preceding. It liberates hæmoglobin from the corpuscles, and causes hæmoglobinuria; but morphological remains (Schatten, etc.) also soon appear, and there is usually slight icterus.

This explanation of the differences in the action of different substances on the blood is adopted by Silbermann.¹

Stadelmann² hesitates to accept it, but cannot altogether reject it. It may be sufficient, he thinks, to account for the jaundice, but it is quite insufficient, in his opinion, to explain the degree of jaundice. He considers that the blood corpuscles of different species of animals have a different resisting power towards different poisons; but any essential difference in the nature of the action of different poisons on the blood he could not discover. Individual differences there undoubtedly are. Thus in dogs, arseniuretted hydrogen causes intense hæmoglobinuria and well-marked changes in the blood (altered corpuscles, Schatten, etc.), while with toluylenediamin signs of blood destruction are infrequent. But this is not constant. Every now and again a case is met with in which the latter drug causes intense hæmoglobinuria without jaundice, although the morphological changes in the blood are the same as those which usually attend its action when it causes jaundice.

X. AUTHOR'S OBSERVATIONS.

My observations on this point relate to the action of distilled water, glycerine, pyrogallie acid, and toluylenediamin, but more particularly to the last.

With regard, first of all, to the modes of action of the above agents on the blood, my observations confirm in the main those of Afanassiew regarding the differences in the blood changes in the case of individual drugs.

I do not find, however, that these differences are of such a character, either in degree or in kind, as to account for the very different action of the agents qua the production of jaundice.

As regards *glycerine*, this agent is, in my opinion, unsuitable for comparison experiments with such agents as pyrogallie acid or toluylenediamin. When injected subcutaneously, as in Afanassiew's experiments, it produces intense inflammatory œdema; and much of the hæmoglobinæmia is due to its action on the red corpuscles at the seat of injection. The œdematous fluid is hæmoglobin-tinted.

A much more suitable agent of this class, I consider, is *distilled water* injected directly into the circulation. It likewise dissolves the hæmoglobin from the corpuscles, leaving apparently few morphological remains in the blood. At least this is the case, judged by the appearances presented in the circulating blood during life.

¹ "Ueber Hæmoglobinæmie," *Ztschr. f. klin. Med.*, Berlin, 1886, bd. xi. s. 471.

² *Op. cit.*, s. 237.

Few or no changes are presented in the circulating blood even after the injection of large quantities of distilled water (70 c.c., Exp. 48), notwithstanding that a great destruction of blood may have taken place. Thus, in Exp. 47, the hæmoglobin was reduced in amount by one-seventh in the course of 24 hours. In Exp. 48 there was intense hæmoglobinuria. If, however, the animal be killed within a few hours of the injection (Exp. 88), numerous stromata are found, especially in the capillaries of the liver (Exps. 47, 48, 88).

EXPERIMENT 47.—RABBIT; under observation for a week; red corpuscles, 5,650,000; hæmoglobin, 70 per cent.

Oct. 7. 1.30 P.M.—50 c.c. distilled water injected into jugular vein.

3 „ No débris, or schatten, or stromata in blood examined; pure.

Blood examined in $\frac{3}{4}$ per cent. NaCl shows a considerable quantity of granular débris, small colourless spherules; no schatten.

„ 8.—Red corpuscles, 5,480,000; hæmoglobin, 60 per cent.

Animal recovered, eating as usual.

Urine, 50 c.c.; large quantity of yellowish remains of hæmoglobin.

„ 10.—Red corpuscles, 5,290,000; hæmoglobin, 58 per cent.

Killed 3 days after operation.

Liver.—Cells fatty, especially in portal zone; free from blood pigment particles; no darkening in sulphide of ammonium.

Spleen.—Slight darkening in NH_4HS .

Bone marrow not affected by NH_4HS ; no excess of pigment.

EXPERIMENT 48.—RABBIT.

Oct. 10. 3 P.M.—70 c.c. distilled water injected into jugular vein.

4 „ No changes recognisable in corpuscles; no schatten; a little granular débris.

„ 11. 12 noon.—Red corpuscles show no abnormality; no granular débris; no schatten.

Urine contains large quantity of free hæmoglobin, and casts and granular remains of hæmoglobin.

„ 12. 11 A.M.—Killed (44 hours after operation).

Spleen considerably enlarged. A large number of red corpuscles present bud-like projections; a large quantity of colourless granules seen; detached buds are seen floating about, and also enclosed in splenic cells; distinct increase in blood pigment.

Liver.—Red corpuscles normal; no appearance of buds; liver cells fatty; no sign of blood pigment; no darkening in sulphide of ammonium.

Red bone marrow.—Blood corpuscles normal in appearance; no buds; a few pale stromata seen. Little or no darkening in NH_4HS .

EXPERIMENT 88.—RABBIT; 70 c.c. of distilled water injected into jugular vein; death 2 hours later; intense hæmoglobinuria.

Blood of portal vein.—Corpuscles pale, but no granular débris or obvious disintegration of corpuscles.

Splenic vein.—Corpuscles pale, but no granular débris or obvious disintegration of corpuscles.

Spleen.—Red corpuscles, for the most part apparently normal; a few show-

ing small bud-like projections; but little granular débris, and only a few pale colourless spherules.

Liver.—Marked polycholia; upper intestine filled with yellow bile; within capillaries great numbers of partially or completely decolorised stromata and colourless spherules.

In addition, very numerous small yellow spherules; not fat, resembling similar particles in the liver cells.

Spleen.—Contrast very great. Red corpuscles almost all normal, only a few showing small bud-like projections; very little granular débris, and only a few pale spherules.

After *pyrogallie acid*, large numbers of schatten are to be found in the blood if the dose be large (Exp. 58). At no time, however, are the number of schatten in the circulating blood at all proportional to the diminution in the number of red corpuscles. Moreover, with small doses, a large destruction may, I find, take place without any schatten formation at all, and with as little evidence of change in the blood as is found after injection of distilled water (Exp. 54).

EXPERIMENT 58.—RABBIT.

Date.	Weight.	Number of Red Corpuscles.	Changes in Red Corpuscles in Circulating Blood.	Remarks.
Nov. 11. 12 noon.	3050	6,280,000	Normal.	1 gramme (.33 per kilo) pyrogallie acid in 10 c.c. ($\frac{3}{2}$ per cent. NaCl) injected subcutaneously.
1.30 P.M.	...	5,950,000	Corpuscles quite normal.	...
5 P.M.	...	6,240,000	Corpuscles quite normal. Not a sign of blood destruction.	...
Nov. 12.	3050	6,300,000	Not a sign of blood destruction.	Animal depressed.
Nov. 14.	2850	5,790,000	Not a sign of blood destruction.	...
Nov. 16. 12 noon.	2850	5,890,000	...	1.5 gramme (0.52 per kilo) pyrogallie acid in 15 c.c. NaCl solution injected intravenously.
2.30 P.M.	...	5,560,000	Red corpuscles show no budding or fragmentation. No schatten.	...
5.30 P.M.	...	4,650,000	Small spherical fragments seen.	Circulation feeble, difficulty in getting blood.
Nov. 17.	2650	1,100,000	Extraordinary number of schatten, almost equalling in number the red corpuscles. The blood is dark in colour, watery in consistence. The absent corpuscles are by no means represented by their schatten. Great increase in number of leucocytes.	Animal apparently well. Urine 140 c.c., highly albuminous, and containing large quantity of remains of blood. No Gmelin's reaction.

EXPERIMENT 58.—RABBIT—*continued.*

Date.	Weight.	Number of Red Corpuscles.	Changes in Red Corpuscles in Circulating Blood.	Remarks.
Nov. 18.	2550	550,000	Blood very watery. Corpuscles form rouleaux imperfectly. Enormous increase in leucocytes—as many as fifty in a sparsely-filled field. Schatten in great number, although not so numerous as yesterday. Large quantity of granules; red corpuscles seen throwing off bud-like projections.	Animal looking very ill and anæmic.
Nov. 19.	2550	590,000	Blood very thin and watery; has lost its dark colour; shows a very large number of granules, and more marked alterations in red corpuscles. Schatten still to be seen, but much fewer in number. Leucocytes much fewer—fourteen in a field. A number of the red corpuscles are extremely large—pale, bi-concave—twice to three times larger than others. Some of them showing long processes (pear-shaped).	Very ill and feeble. Killed at 12.

EXPERIMENT 54.—RABBIT.

Date.	Number of Corpuscles.	Changes in Blood.	Remarks.
Nov. 4. 11.20 A.M.	5,850,000	None.	0.5 gramme pyrogallie acid in 10 c.c. NaCl solution, injected subcutaneously.
12.20 P.M.	5,090,000	No changes.	...
3.20 P.M.	5,150,000	No changes. No schatten.	...
Nov. 5.	4,240,000	No changes. No schatten.	...
Nov. 7.	4,400,000		Animal apparently in good health. Killed with ether.

Spleen becomes coal-black in sulphide of ammonium; contains a very large quantity of iron pigment.

Liver.—Very rich in blood; no blood pigment in cells; no darkening in NH_4HS .

After *toluylenediamin* poisoning there is less tendency to the formation of schatten, at least in dogs and rabbits. The red corpuscles seem rather to break up into yellow spherical particles—these may be seen in process of being thrown off as bud-like projections from the red corpuscles.

This process goes on especially in the spleen, according to my

observations. So much so indeed, that as I have elsewhere shown,¹ the removal of the spleen in rabbits diminishes, materially, the destructive action of toluylenediamin.

In cats, however, I find schatten formation is as marked a feature of toluylenediamin poisoning as it is of pyrogallie acid poisoning. Conversely, with pyrogallie acid I have found in some cases, along with formation of schatten, the red corpuscles throwing off buds in precisely the same way as is usually found after toluylenediamin (Exps. 45, 46, 55).

EXPERIMENT 45.—YOUNG RABBIT.

Sept. 29, 12.30.—0.25 gramme toluylenediamin in 5 c.c. $\frac{3}{4}$ per cent. solution NaCl subcutaneously.

„ 30. —Animal unaffected; killed 12.30.

Liver.—A very distinct excess of fine granular blood pigment in cells, especially in portal zone, blackened with NH_4HS .

Spleen.—Very little darkening with NH_4HS ; no apparent increase of blood pigment.

Bone marrow of femur.—No abnormal appearances. Slight darkening in NH_4HS ; but no apparent increase of pigment microscopically.

EXPERIMENT 46.—YOUNG RABBIT.

Sept. 29, 12.30.—0.5 gramme toluylenediamin in 10 c.c. NaCl injected subcutaneously.

2.30.—Animal affected; looking rather ill, and lying down.

Blood shows no changes; no schatten or granules.

„ 30. —Purged during the night; depressed.

12.30.—Killed.

Liver.—Cells fatty; a very distinct excess of granular pigment; most of all in cells of portal zone; granules blackened by NH_4HS .

Spleen.—Pale and anæmic and contracted; shows a large number of yellow granules; little darkening in NH_4HS .

Bone marrow.—Slight over-darkening in NH_4HS ; microscopically, a number of yellow granules.

EXPERIMENT 55.

Date:	No. of Red Corpuscles.	Morphological Changes in Blood.
Nov. 10 . . .	6,000,000	None.
„ 12 . . .	6,110,000	„
„ 16 . . .	6,220,000	„
„ 16, 1 P.M. .	0.75 gramme toluylenediamin injected intravenously	„
„ 16, 3 P.M. .	6,105,000	One or two fading corpuscles seen; also few pale spherules.
„ 16, 6 P.M. .	6,080,000	No schatten; a considerable number of small spherical bodies seen, some throwing off bud-like processes.
„ 17, 11 A.M. .	4,970,000	Corpuscles perfectly normal in shape and appearance; no schatten; no granules.
Killed, 12 A.M.		

¹ *Lancet*, 1892, ii.

Spleen.—Not enlarged, or presenting any appearance of congestion. A considerable number of the red corpuscles show bud-like outgrowths, and many of these latter are seen floating about free as small yellow globules; no schatten.

Tissue becomes coal-black in sulphide of ammonium; microscopically, pigment in form of minute spherical granules of varying size, mostly free, but many lying within cells.

Liver.—Lobules mapped out by pale centres and congested margins. Cells are fatty; hardly any darkening in sulphide of ammonium.

Bone marrow.—No increase of pigment; no darkening in NH_4HS ; no appearance of budding in red corpuscles; a few small spheres, almost colourless, seen.

It will be noted that the chief evidence of the undoubted blood destruction (fall in the red corpuscles from 6,220,000 to 4,970,000 in 24 hours) was to be found in the spleen in the form of budding corpuscles, and great excess of blood pigment. No schatten were to be found.

Certain differences are thus observable in the *mode of action* of destructive agents on the blood corpuscles. But they are not so distinctive either as regards their character or degree as to explain the remarkably different action of these drugs in the production of jaundice. They are of some importance as serving to explain the occurrence or non-occurrence of hæmoglobinuria. But they serve in no way to explain the point at issue, namely, why in one case jaundice should occur where there is not even any hæmoglobinæmia, and is absent when the latter is pronounced.

The character of the blood changes not being sufficiently distinctive to account for the presence or absence of jaundice, we have to look elsewhere.

Another view suggests itself, namely, that the occurrence of jaundice may be influenced by the *character* of the hæmoglobin.

Lauder Brunton has suggested in the same relation that the differences observable in different animals may indicate differences in the relation of hæmoglobin to the liver cells in different classes of animals.¹

That individual differences exist in the character of the hæmoglobin of, *e.g.*, the dog, the cat, and the rabbit respectively, is, I think, exceedingly probable. The hæmoglobin of one has a poisonous action when injected into the other. But that these of themselves are sufficient to account for the differences as regards liability to jaundice in these animals is, I think, extremely improbable. Much more depends, in all probability, on the natural degree of concentration of the bile in these different animals. In the rabbit, *e.g.*, the bile is normally much more watery than in the dog, and its quantity is much greater. A factor, therefore, which in a dog might occasion such a degree of concentration of the bile as to lead to a temporary arrest in its flow, and to jaundice, might quite well be without any influence in the rabbit.

¹ Murchison's "Diseases of the Liver," 3rd edition, ed. by T. Lauder Brunton.

As a matter of observation, I have never noticed in rabbits any condition which could rightly be termed jaundice produced by action of destructive agents on the blood. Hence, as regards jaundice, comparisons between rabbits and dogs are inapt. The latter are as naturally subject to some degree of jaundice as the former are naturally immune; and this I consider arises not so much from any differences in the *character* of the hæmoglobin in the two cases, or in its *relation* to the liver cells, as from radical differences connected with the habits as regard food, etc., and metabolism of the two animals.

A third alternative suggests itself, namely, that the occurrence or non-occurrence of jaundice after an increased blood destruction may be dependent on the *form* in which the hæmoglobin is supplied to the liver. Thus, after the action of distilled water the hæmoglobin is liberated from the stroma of the corpuscle, and passes freely into the urine. After toluylenediamin the red corpuscles break up into yellow globules in a manner almost identical with their behaviour under the influence of high temperatures as described by Max Schultze.

That the hæmoglobin is supplied to the liver cells in different forms in these two cases is, I consider, certain from other evidence. It is the latter form of hæmoglobin that, according to my observation, most of all favours the formation of blood pigment both in liver cells and in spleen; and this, too, in different classes of animals alike—dog, rabbit, and pigeon, while, according to my observations, free hæmoglobin, such as is produced by distilled water, does not lead to the formation of blood pigment, either within liver cells or spleen (*vide* Exps. *antea*).

Under the action of toluylenediamin, then, the hæmoglobin does not, I conclude, become dissociated from the albuminous stroma of the corpuscle, as is the case with distilled water. It is found in the form of yellow droplets or spheres within the blood, within the spleen. In this form also it passes through the kidneys; not, however, as free hæmoglobin—for, notwithstanding the presence of much of this material in the urine, the urine gives none of the reactions of free hæmoglobin. There is no hæmoglobinuria in the ordinary sense of the term.

Similarly, in this form also the hæmoglobin reaches and passes into the liver cells.

It is, I think, important to note these physical peculiarities in the action of toluylenediamin on the blood corpuscles, and especially on the hæmoglobin of the blood. For although their bearing on the pathology of the jaundice caused by this drug may not be clear, they nevertheless may have some significance, as denoting changes of a more obscure chemical nature in the character of the hæmoglobin supplied to the liver in such cases. This at least, in my opinion, is the only possible direction in which the occurrence of jaundice may be affected by the *character* or *form* of the hæmoglobin supplied to the liver. But while admitting this, I do not consider it at all likely that such is the case. Nor do I consider that change in the character of the hæmoglobin is

sufficient to account for the changes in the bile which occasion the jaundice of toluylenediamin poisoning.

For the action of this poison on the blood is, according to my observations, identical in dogs and rabbits. Moreover, what is of more importance, is that in the rare cases in dogs, in which this drug causes hæmoglobinuria without jaundice, the changes in the blood are of the same character, differing only in degree, as those found when jaundice occurs without hæmoglobinuria (Stadelmann).

I consider, then, that some other factor than mere *quantity* or *character* of the hæmoglobin, must be responsible for the increased viscosity of bile produced by the drug.

And these being excluded as insufficient, there remains only to be considered one further possible factor—the influence, namely, of the poison itself—exerted not on the liver cells, as suggested by Stadelmann, nor on the blood, as supposed by Afanassiew, but on the biliary channels in course of its excretion, as I have shown.

So far as toluylenediamin itself is concerned, I consider that the effect of the catarrh resulting from its excretion (either of itself or of its products) in causing obstruction is fully established by the foregoing observations. And it is in this direction that the explanation of the differences in the behaviour of various blood-destroying agents, *qua* the production of jaundice, is, in my view, to be sought.

I have shown that neither hæmoglobinæmia nor (however intense) mere increase of bile pigments (polychromia) can account for the increased viscosity of bile which occasions the jaundice. The latter may be intense with only a half increase in the bile pigments (toluylenediamin), or only slight, possibly absent, with a threefold or fourfold increase (arsenious acid); or may be absent altogether with the intense hæmoglobinæmia occasioned by distilled water.

I have also shown that, in my opinion, change in the *character* of the hæmoglobin, although conceivably a possible factor, is not a probable one in bringing about the essential changes in the bile necessary for the production of obstruction, namely, the increase of viscosity. The only remaining factor, then, is the action of the poison that occasions the blood changes. According to the degree with which this is capable of exciting catarrh of the bile ducts, in course of its excretion, is there liability for the blood-destruction to be attended by jaundice.

XI. NOMENCLATURE.

The jaundice so produced is *hepatogenous*, inasmuch as it is due to obstruction occasioned by this increased viscosity of the bile. It may also be termed "*hæmo-hepatogenous*," as suggested by Afanassiew, inasmuch as it is preceded by changes in the blood. The term "*hæmatogenous*" has, however, been used in connection with jaundice in a special sense, as implying that the bile pigment itself is formed in the

blood, that its use in any other sense is apt to mislead. And hence the above term, although not inappropriate, is, in my view, open to objection on that ground.

To avoid this difficulty, Quinke has proposed the name *an-hepatogenous*, thereby denoting that while the jaundice is essentially hepatogenous, it is nevertheless closely related to, and dependent upon, other changes elsewhere (in the blood).

Stadelmann, as we have seen, regards the essential and most constant change as the increase of bile pigments; and the jaundice which results might, in his opinion, be mostly termed "*polychromic*, or "*jaundice from polychromia*."¹

I have endeavoured to show in the foregoing that this name is inappropriate, inasmuch as increase of bile pigments cannot be regarded as the essential change in the bile, or the chief factor in causing the obstruction.

So far as the bile pigments are concerned, identical changes, differing only in degree, are produced by agents so widely differing in their action *qua* jaundice, as normal saline (0·8 and 0·6 per cent.) solutions, salicylate of soda, distilled water, arseniuretted hydrogen, pyrogallie acid, phosphorus, and toluylenediamin. Thus normal saline solution (0·8 per cent.) may, as shown by Stadelmann, cause an increase of one-third in the bile pigments (bile acids being diminished to one-fifth or one-seventh)—changes, therefore, hardly less striking than the increase of one-half in the bile pigments (with bile acids reduced at first to one-half then to mere traces), which occurs in toluylenediamin poisoning; or the increase of one-half in the first 10 hours in phosphorus poisoning (with diminution in bile acids); or, lastly, the three-and-one-half-fold increase with arseniuretted hydrogen.

Clearly, then, a condition (polychromia) which is not proportional to the degree of obstruction cannot be regarded as the essential condition occasioning the obstruction. And that this is the case Stadelmann himself freely admits. While maintaining that the term polychromia best describes the jaundice, he admits that other factors must operate to bring about the change in the character of the bile itself on which the obstruction depends; and these factors are, in his view, to be sought for in a direct action of the several poisons on the liver cells, leading to a production of a highly concentrated bile.

It may, perhaps, seem a matter of comparatively little moment what name be given to this form of jaundice. I cannot, however, so regard it. The terms "*hæmatogenous*" and "*non-obstructive*," formerly and still in many cases applied to it, are no longer applicable, inasmuch as the jaundice is not hæmatogenous, but essentially hepatogenous and obstructive.

The term hepatogenous, therefore, fully describes its character anatomically. It is due to obstruction and to reabsorption of bile

¹ *Op. cit.* p. 247.

pigments, just as ordinary obstructive jaundice is. But it differs totally from the latter in its pathogeny; and some title is wanted to designate its relationship with the disorder of the blood with which it is ordinarily associated.

So far as toluylenediamin is concerned, the obstruction, as I have shown, is essentially of catarrhal origin; and the term "catarrhal jaundice" might, in my opinion, quite fitly and appropriately be given to it, but for one circumstance, namely, that this designation has come to be applied to, and reserved for, a form of jaundice of essentially different origin. Ordinary so-called catarrhal jaundice is, by a general consensus of opinion, supposed to arise from catarrh of the duodenum, involving the orifice of the bile duct secondarily. In no other sense, for example, is it spoken of by Murchison.

In the present case the course of the catarrh is quite a different one. It begins in the origin of the bile ducts, and extends downwards. If the duodenum is at all involved, and it is only in severe cases that it does become involved, it is only secondarily to the catarrh in the bile ducts.

It may perhaps be a question how far so-called catarrhal jaundice does arise in the way described, namely, secondarily to duodenal catarrh—to what extent it may not rather arise primarily in the bile ducts. In my opinion it is a very open question indeed. The latter I am disposed to regard as in all probability the common mode of origin of catarrh of the bile ducts.

But such a view is at variance with that commonly accepted, which regards catarrhal jaundice as arising secondarily to catarrh of the duodenum; and under these circumstances I do not consider that to apply the term "catarrhal" in a sense entirely different would be fitting.

Moreover, the term catarrhal, however appropriate, would not indicate the special feature of this variety of jaundice, namely, its relation to previous disorder of the blood.

That disorder, in the great majority of cases, is marked anatomically by increased destruction of blood (hæmolysis); and the term therefore which, in my opinion, would most fitly describe its character, would be that of "hæmolytic jaundice."

And yet even this term is not altogether free from objection.

It is true that increased hæmolysis accompanies and precedes in most cases the form of jaundice now under consideration, whether induced experimentally by destructive agents, such as water, ether, pyrogallie acid, toluylenediamin, etc., or occurring clinically in paroxysmal hæmoglobinuria, pernicious anæmia, malaria, yellow fever, icterus gravis, etc.

But, as I have shown, it is not the increased hæmolysis *per se*—with its hæmoglobinæmia or the associated polychromia—that can be held accountable for the jaundice; but rather is it that both the hæmolysis and the jaundice have one common factor.

The factor that occasions the catarrh on which the jaundice depends is, in my opinion, the poison; hence, on this view, the term which would in all respects most aptly describe this form of jaundice would, in my opinion, be the term "toxæmic."

It is free from the objection to which, as I have shown, the term *hæmo-hepatogenous* is open. It has the advantage over the term *hæmolytic*—which, in most respects, would be a very suitable one—in being, I consider, more generally accurate, and more closely indicative of the nature of the relationship between the jaundice and disorder of the blood. Lastly, it has the advantage of being not only appropriate as regards the pathogeny of the jaundice, but also as regards its features clinically, and the general clinical course it pursues. It is in toxic conditions generally—in pyæmia, yellow fever, epidemic jaundice, icterus gravis, etc.—that this variety of jaundice is generally met with.