

On the bile : jaundice & bilious diseases.

Contributors

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ON THE BILE

JAUNDICE

AND

BILIOUS DISEASES

BY
J. WICKHAM LEGG

FELLOW OF THE ROYAL COLLEGE OF PHYSICIANS OF LONDON
ASSISTANT PHYSICIAN TO SAINT BARTHOLOMEW'S HOSPITAL AND LECTURER ON PATHOLOGICAL
ANATOMY IN THE MEDICAL SCHOOL

La bile est un liquide dont l'étude intéresse au plus haut point le physiologiste et le médecin. Les difficultés dont est entouré son histoire physiologique font qu'elle est encore fort obscure.

CLAUDE BERNARD.

NEW YORK
D. APPLETON & Co., 1, 3 & 5 BOND STREET.
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To

HIS ROYAL HIGHNESS

THE PRINCE LEOPOLD

The following pages are, with all respect, inscribed, in
grateful acknowledgement of many favours,

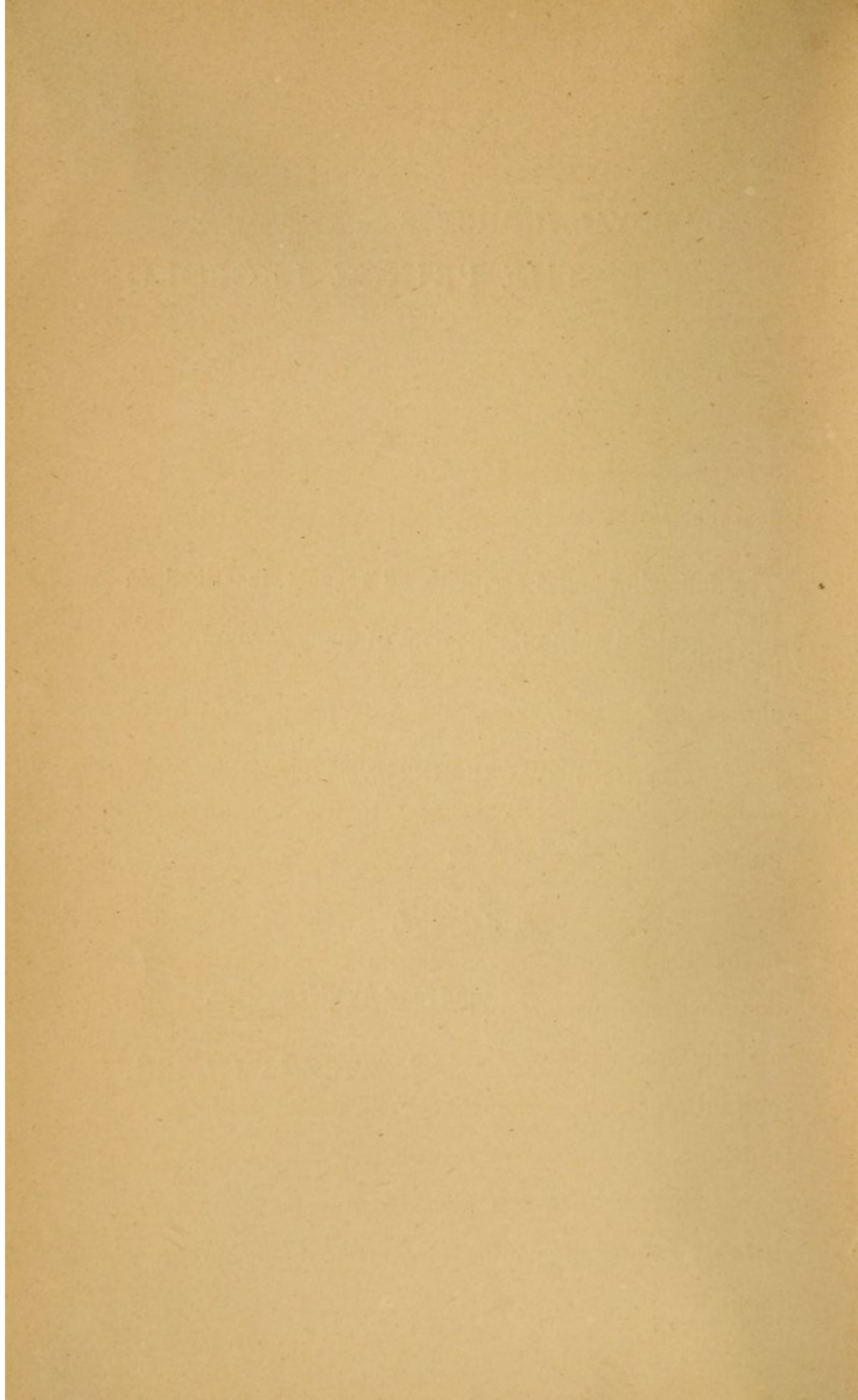
by HIS ROYAL HIGHNESS'

most dutiful,

most devoted,

and most humble servant,

J. WICKHAM LEGG.



PREFACE

THE liver is the largest gland in the body; and its importance to the animal œconomy is shown by its presence in the lowest tribes, and by its early appearance in the developement of the embryo. It might be looked for that an organ so large and so constantly seen should be endowed with manifold functions; but for the demonstration of these we have had to wait almost to our own time, for it is hardly more than thirty years ago since Claude Bernard began a series of discoveries, which have ended in the restoration to the liver of all the functions which it formerly possessed, according to the speculations which we find recorded in the writings of Galen. That these functions become disturbed in disease is a proposition of great likelihood; and the liver may hereafter prove one of the most important of the organs concerned in all matters of nutrition, growth, sanguification, and animal life. But as so short a time has gone by since these functions became known in health, very little, if any, progress

has been made in the knowledge of the changes which they undergo in disease. Some observations made at St. Bartholomew's Hospital in the year 1873, on the amount of glycogen in the liver in jaundice, are among the first attempts to tread this path of experiment.

The following pages are devoted to that office of the liver which, for two hundred years, was the only one allowed by physiologists; that is, the secretion of bile. The early chapters treat of the chemistry and physiology of this humour. The first of these may be thought to be in a tolerably satisfactory state, since so much light was thrown upon the chemistry of the bile acids by the labours of Adolf Strecker thirty years ago. The physiology of the bile is still surrounded by a darkness almost Egyptian; and it may surprise many to find how little knowledge there is of a humour which has been carefully studied for over two thousand years, and which already filled a great place in the physiology of the *Timæus*. Much of this obscurity is doubtless due to the place which physiology holds among the sciences; little progress can be made till the others beneath have well nigh reached perfection; and still more to the point at which the bile is dis-

charged, into the upper part of the intestine, where it cannot conveniently be collected and measured, as may readily be done with other secretions, such as the urine. A bar, not to be overcome, seems to be thus placed by nature herself in the way of much increase of knowledge.

In several chapters, the phænomena caused by an obstruction to the discharge of the bile into the intestine have been dealt with ; and in those which follow, an account has been given of certain species of jaundice, where an obstruction to the flow of bile cannot at once and without trouble be discovered after death. And to those species of jaundice, the cause of which is obscure, I have confined myself ; though, nevertheless, I have not fallen into the un-English virtue of consistency ; for, as part of the chapter on *icterus infantum*, I have dealt with the appearances which follow congenital constriction of the gall ducts, which may by some be considered only a variety of the foregoing *icterus*. In a work, too, which deals with disorders of the bile, some account of gall-stones might be looked for ; but the space required for anything like a full discussion of the phænomena caused by these bodies would be very great, and I have

already gone beyond the bounds which were set when the printing of this book was begun. Sometimes, too, I have had to travel twice over the same ground in dealing with the physiology of the bile and the doctrine of jaundice; and there thus arises the appearance of repetition, very needful, however, to the right understanding of the matter in hand.

In the last chapter I have specially considered the meaning of "bilious diseases"; and I have proposed that the word "bilious" should no longer be used as an adjective to diseases. I am led to this proposal by the great confusion which exists as to the definition of the word; nearly every country, and I might say, nearly every author, having a different sense for it. In this work, "bilious," when used with the word headache, attack, or the like, always connotes a gastric catarrh.

I am glad of this opportunity to thank Professor Chauveau and the French Government for the hospitality shown to a foreigner in providing the means for some experiments which were made at Lyons nearly two years ago, and of which I have spoken in the fourteenth Chapter of this work. All the appliances of one of the best furnished laboratories in Europe were set before me; a

staff of able assistants was told off to give me whatever aid was needful ; and the cost of the whole series of experiments was borne by the French Government. It would be indeed ungrateful not to acknowledge, even in this feeble way, the welcome which I received. It may strike others, besides myself, that much light would have been thrown upon many other points in this work by well-devised experiments. But in England, for some years past, all experiments on animals have been practically forbidden. We pay for our freedom in some matters by being at the mercy of every truculent agitation in others ; and a senseless outcry, by putting on the sacred garb of religion and morality, from the highest authorities in which it receives no countenance, but rather condemnation, has prospered in its designs for a time. In the plan of the book I have therefore followed the method of Albert the Great, rather than the higher path shown us by Francis Bacon, and our own great predecessor at St. Bartholomew's, William Harvey. For whatever imperfections there may be in the method followed, the reader must blame those Manichæan teachings, which, harmful as they are, are almost as old as the human race itself, and the germs of which seem to exist

everywhere, ready to burst into a fresh life, even amongst those who claim to be most orthodox and sincere in their morals and belief.

London, Dec. 20, 1879.

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ERRATA.

p. 72, Heinrich Bayer's paper on human cholalic acid appears in the September number of Hoppe-Seyler's *Zeitschrift f. phys. Chemie*, 1879.

p. 148, second line from top, for *chloidic* read *choloidic*.

p. 485, third line from top, for *blood from the urine* read *blood from the arm*.

p. 491, third line from top, for *Morand* read *Morand*.

CHAPTER I.

CHEMISTRY OF THE BILE.

THE bile of vertebrates is made up chiefly of three groups of bodies: the bile acids in combination with soda; the bile pigments; and fats, especially cholestearin. Of these, the bile acids are by far the most noteworthy, as they are found in greatest amount, and are the most important in their physiological action and relations.

It cannot be looked for that much information should have been gained as to the chemical composition of the bile before the time of Lavoisier. But it needed no chemist to say that the bile held a pigment: and it was well known that it possessed the power of cleaning stuffs like a soap.* Robert Ramsay appears to have been the first to note the resin in the bile which was afterwards to be known as the bile acids,† but it is to the very beginning of this century that we must look for the first satisfactory attempts at an analysis of the bile.

Thenard, by throwing down the bile with the acetate of

* Cadet, *Mémoires de l'Académie royale des Sciences*, année 1767, Paris 1770, p. 483. "Je puis donc enfin conclure que la bile est un véritable savon composé d'une graisse animale et de la base alcaline du sel marin, et du sel marin lui-même, d'un sel essentiel de la nature du sucre de lait et d'une terre calcaire qui participe un peu du fer." For history of earlier opinions, see Haller, *Elem. phys.* Lugd. Bat. 1764, t. vi. p. 542. Lib. xxiii. § iii. For history up to his own time, see Platner, *Ueber die Natur u. den Nutzen der Galle*, Heidelberg, 1845.

† Roberti Ramsay, *Diss. Med. inaug. de bile*, Edinb. 1757, in Sandifort's *The-saurus Dissertationum*, Roterodami, 1769, vol. ii. p. 567. "Bilis materiis constare videtur tribus diversis, parte scilicet aquosa; parte resinosa, spiritu vini, non aqua solubili; parte denique viscida putrescente, neque aqua, neque spiritu vini solu-bili".

lead, an agent which has proved so useful in the manipulation of this humour, obtained a body which he named picromel,* from its taste. This appears to have been a collection of the impure bile acids. He also separated a resin or fat, to which he attributed in chief the colour and taste of the bile. He opposed the ancient belief that the bile was a kind of soap. He noted the amount of soda salts, the presence of traces of iron, and that the solids were about $\frac{1}{8}$ to $\frac{1}{9}$.†

Berzelius followed hard upon Thenard with his investigations on the bile. He thought it probable that the picromel and resin of Thenard were but one body. Berzelius named this biliary material;‡ it was, in his opinion, free from nitrogen but akin to albumen.

Tiedemann and Gmelin report a large number of analyses of the bile in their work on the digestion of animals.§ They claim to have noted the presence of cholestearin in the bile in the year 1823, before they were acquainted with the work of Chevreul, and also to have discovered in the winter of 1823-24 the action of nitric acid on the colouring matter of the bile.|| They also affirmed the presence in the bile of margarates, oleates, acetates, cholates, bicarbonates, phosphates, and sulphates of soda, and a body which they called asparagin but which it is possible was taurin. A few years later, Fromherz and Gugert¶ came to results very nearly allied to those of Tiedemann and Gmelin. Ten years later Demarçay succeeded in separating three

* Apparently compounded of *πικρός*, bitter, and *μέλι*, honey.

† Thenard, *Mémoires de Physique et de Chimie de la Société d'Arcueil*, 1807, t. j. p. 23. Lu à l'Institut le 2. floréal, an 13.

‡ Berzelius, Schweigger's *Journal f. Chemie und Physik*, 1814, Bd. x. p. 488.

§ Tiedemann and Gmelin, *Recherches exp. phys. et chimiques sur la digestion*, Jourdan's trans. Paris, 1826, 1ère partie, p. 42.

|| Preface, p. xv. See Chevreul, *Journal de phys. exp. et path.* 1824, t. iv. p. 257. He certainly found cholestearin in the bile.

¶ Fromherz and Gugert, Schweigger's *Journal f. Chem. u. Phys.* 1827, Bd. l. p. 68.

acids, choleic, choloidic, and cholic, but not in crystals.*

Here the history of the chemistry of the bile may be broken up into three heads: and the chemistry of the bile acids of the pigments, and of cholestearin considered apart.

THE BILE ACIDS, OR BILIN.

Crystallised Bile.—Platner first made out that the resin which bile held was a crystallisable body.† A few years after, Adolph Strecker discovered that this crystallised bile, obtained from ox-bile, was made up of the soda salts of two acids; one, forming the greater part of the compound, an acid containing nitrogen, but free from sulphur, which Strecker in the German tongue called *Cholsäure*; this would be in English, I suppose, cholic acid, but it is to-day very generally called glycocholic acid from its relation to glycocoll:‡ the other held sulphur as well as nitrogen, and was called by Strecker *Choleinsäure*, which in English might be spoken of as choleinic acid; the name now in general use is taurocholic acid from its relation to taurin.§

For the preparation of Platner's crystallised bile I have found a modification of a process recommended by Kühne very serviceable.|| The bile of six or eight ox-bladders is brought together in a large Berlin dish and rubbed up into a black mass with an excess of

* Demarçay, *Annales de chimie et de physique*, 1838, t. lxxvii. p. 177.

† Platner, *Arch. f. Anat. Phys. u.s.w.* 1844, p. 94. See also Liebig's *Annalen d. Chemie u. Pharm.* 1844, Bd. li. p. 105. His work is given at large in his pamphlet published at Heidelberg in 1845: *Ueber die Natur und den Nutzen der Galle*.

‡ The names glycocholic and taurocholic acid appear in the first volume of C. G. Lehmann's *Lehrb. d. phys. Chemie*, second edition, published at Leipzig in 1850.

§ Adolph Strecker, *Annalen d. Chemie u. Pharm.* 1848, Bd. lxxv. p. 1. and Bd. lxxvii. p. 1.

|| Kühne, *Lehrbuch d. phys. Chemie*, Leipzig, 1866, p. 75.

animal charcoal. This black mass is then put into a wide-mouthed bottle, shaken up with ordinary spirit, and allowed to stand for several days. The spirit is then filtered off from the black powder, and the filtrate evaporated to dryness. The dry residue is then dissolved in absolute alcohol and poured into a great excess of æther in a large stoppered bottle. If good crystals be looked for, it is well not to be too sparing with the æther and alcohol. After a few days or even longer, the milky fluid becomes clear, and crystals are deposited at the bottom. I have found this process more serviceable for the manufacture of large quantities of crystallised bile than either the process of Hoppe-Seyler or Kühne. Kühne, for example, evaporates the bile to one-fourth of its volume, then rubs up with animal charcoal, dries the mass at 100° C. then puts the whole, warm, into a large bottle, and exhausts with absolute alcohol. After some days, he filters, and throws down with æther. This is a wasteful method, as so much of the bile acids is retained in the animal charcoal. On the other hand, Hoppe-Seyler does not proceed to decolorise the bile until after the dried bile have been extracted with alcohol. He then evaporates the filtrate to dryness, and dissolves in a small quantity of absolute alcohol, precipitating by excess of æther.* Both these methods succeed on the small scale, but for the preparation of large quantities I prefer the plan mentioned first.

These colourless crystals are composed in the ox of the soda salts of the two acids; they are exceedingly deliquescent, and therefore very soluble in water. They have a peculiar bitter, sweet taste. They are soluble in alcohol, insoluble in æther.

Frerichs and Städeler found that, if the pure soda

* Hoppe-Seyler, *Handbuch d. phys. und path. chemischen Analyse*, Berlin, 1865, p. 149.

salts of the bile acids were acted on by strong sulphuric acid, there was formed at first a colourless mucilaginous mass which dissolved by degrees in the cold into a saffron yellow fluid, with heat into a bright red or brown-red fluid.* These authors thought this observation of much importance, showing the change of bile acid into bile pigment.

It is to the presence of this 'crystallised bile' in the bile that this secretion gives the reaction named after Pettenkofer.† If to a watery solution of the bile acids strong sulphuric acid be added, the bile acids are first thrown down, and then re-dissolved by adding more sulphuric acid. If now a drop of syrup (cane sugar)‡ be added to the warm solution, the temperature of which must not be allowed to rise above 70° C. a fine purple colour is developed; compared by Pettenkofer himself to a solution of permanganate of potash. The development of this colour constitutes Pettenkofer's test. The reaction is given by glycocholic acid, taurocholic acids, and many of their derivatives.

Neukomm found that a watery solution of the bile acids, .4 *per cent.* in strength, gave a fine reaction: with .1 *per cent.* the colour was purple red with a trace of violet: with .04 *per cent.* only a weak wine red colour; and with .01 *per cent.* only a yellow fluid which did not become red on standing. Neukomm thinks that the reaction becomes much more delicate if done in a porcelain dish in the following manner: a drop of the fluid to be tested is let fall into a Berlin dish with another drop of dilute sulphuric acid, one to four, and just a trace of solution of cane sugar added to the

* Frerichs and Städeler, *Arch. f. Anat. Phys. u.s.w.* 1856, p. 55.

† Pettenkofer, *Annalen d. Chemie u. Pharm.* 1844, Bd. lli. p. 90.

‡ Jurasz (*Centralblatt f. d. med. Wiss.* 1875, p. 515) finds that the reaction also appears with grape and fruit sugar, most rapidly of all with this last; slowly with grape sugar. He thinks the ordinary reaction due to the splitting up of the cane sugar by the sulphuric acid into grape and fruit sugar.

whole, and then it is rolled about over the flame of a spirit lamp. The heat used for the evaporation must be small. As the fluid evaporates, a fine red purple is developed. Neukomm says that in this way he has detected $\cdot 006$ of a milligramme.*

Other modifications of Pettenkofer's test have been introduced, notably by Bogomoloff and Strassburg. Bogomoloff recommends that the bile acids be dissolved in alcohol, or that the watery solution have a great excess of alcohol added, and then evaporated over a water-bath in a porcelain dish, moving the dish gently about so that the bile acids may form a tolerably even coating over the dish. A drop, or two, of sulphuric acid is now let fall by means of a glass rod upon the dried bile acids, and in the same place a drop or two of spirit. A number of colours appear. In the centre, the colour is yellow, then around, first orange, then red, rose red, violet, indigo violet, indigo blue; lastly the whole spot becomes blue. By this method Bogomoloff says he has detected 3 milligrammes of bile acid in 15 C.C.†

Strassburg recommends another way, chiefly for the testing of urine. A little cane sugar is added to the fluid, and a piece of filtering paper is dipped into the mixture. The filtering paper is then dried, and on it is let fall a drop of strong sulphuric acid by means of glass rod; in a quarter of a minute a violet colour appears around the drop of acid.‡ I cannot say that I have found this a trustworthy modification. A purplish colour may be seen in urine from many persons not known to be seriously disordered. Strassburg says he has detected $\cdot 00003$ grm. of bile acid by this method.

* Neukomm, *Annalen d. Chemie und Pharmacie*, 1860, Bd. cxvi. p. 30.

† Bogomoloff, *Centralblatt f. d. med. Wiss.* 1869, p. 486.

‡ Strassburg, *Arch. f. d. ges. Phys.* 1871, Bd. iv. p. 461.

A red or purple colour is given by many other bodies besides the bile acids. Pettenkofer himself noted that the reaction appeared with a solution of albumen, but not of mucus:* an observation which was confirmed by Max Sigm. Schultze, who found that muscular tissue, voluntary or involuntary, the crystalline lens, the nerve fibres, and ganglia, showed a red colour with sulphuric acid and sugar. The colour did not appear with tendons or connective tissue, so that the tissues rich in albumen gave the reaction, but not those rich in gelatin.† Beneke has noted the same appearance with chemically pure oleic acid, and with pure æther, and also under certain concentrations with cholestearin.‡ Schneider, too, finds that morphia and cadeia give the same reaction, but not narcotin, nor narcein, quinine, strychnia, brucia, atropia, colchicin, emetia, or picrotoxin.§ The reaction is said also to appear with amylic alcohol.

Koschlakoff and Bogomoloff, noting this false Pettenkofer's reaction with albumen and other bodies, say that the spectrum affords a sure means of diagnosis. The fluid of Pettenkofer's reaction is so deeply coloured that it must be diluted before light can pass through. This dilution is best done with acetic acid, as water throws down a violet precipitate. This fluid in the spectroscope shows with moderate concentration four absorption bands; the largest and most intensely marked, shows itself in E and a little to the left. The other in F. The third between D and E, nearer to

* Pettenkofer, *loc. cit.*

† Max. Sigm. Schultze, *Annalen d. Chemie u. Pharmacie*, 1849, Bd. lxxi. p. 273. Like observations have been made on the tissues of invertebrate animals by Friedrich Will (*Arch. f. Anat. Phys. u.s.w.* 1848, p. 502), and Voit (*Zeitschrift f. wiss. Zoologie*, 1860, Bd. x. p. 470.)

‡ Beneke, *Studien ueber das Vorkommen, die Verbreitung und die Function von Gallenbestandtheilen*, u.s.w. Giessen, 1862, pp. 35 et seq.

§ Schneider, *Annalen der Physik und Chemie*, 1872, Bd. cxlvii. p. 128.

D. The fourth near D. If the fluid be more dilute, the bands in E are well seen, between D and E much less marked, and in D and F very weak. With high concentration, the absorption bands in E and between D and E unite in one plainly marked band. In F there is a well-marked band. In D the bands are always well marked.

These observers also remark that the fluid of Pettenkofer's reaction shows a fluorescence, if well diluted with dilute acetic acid; it is green by reflected light; cherry red by transmitted light.* This observation has been repeated by Schenk; and he also finds absorption bands in the fluid of Pettenkofer's test, but they are somewhat different in place and number from those noted by Koschlakoff and Bogomoloff. If the solution be dilute there is seen at F an absorption band which fills about half the space between E and F; there is another band at the line E between D and E, and it fills half of this space. But if the solution be concentrated there is only seen one band between D and E.†

Dalton also found absorption bands in the alcoholic solution of Pettenkofer's reaction; two wide and dark bands, one at E, from D 50 E to E 25 F; the other at F, from E 60 F to F 15 G, the spectrum ending about G. A band at D was also frequently seen.

The solution in alcohol of the bile acids shows a spectrum in which the bands at E and F are visible and often also the band at D. It makes a great difference if alcohol or water be used as a solvent: the watery solution gives only one band at E. Beyond the bands the spectrum is dim.

* Koschlakoff and Bogomoloff, *Centralblatt f. d. med. Wiss.* 1868, p. 529.

† Schenk, *Anatomisch-physiologische Untersuchungen*, Wien, 1872, p. 47. I have not been able to find the observations of Waterman, as quoted by Schenk. On the contrary, Waterman says (*New York Medical Record*, 1871-2, Vol. vi. p. 436.) that normal bile is nearly devoid of the power of affecting the spectrum

There is no difference between the spectra of glycocholate or taurocholate of soda.

Dalton thinks that the characters of the spectrum of the fluid of Pettenkofer's reaction may be used to distinguish it from the red fluids obtained by a like reaction on morphia, albumen, and the like. He finds that the opium alkaloids give a band at E, but it is somewhat indistinct and disappears on dilution. Albumen gives a single band in the space between E and F, the edges are not well defined and the spectrum beyond is dim.* Bogomoloff finds that the spectrum of oil treated with Pettenkofer's method gives two bands: one, more intense than the other, between D and E, nearer to D: the other on the left of D.†

Glycocholic acid. For the knowledge of this acid we are indebted to Strecker, and according to his advice it is prepared by dissolving the crystallised bile from ox-bile in water and then throwing down the pure acid with dilute sulphuric acid. The addition of acid must be stopped as soon as a slight precipitate be formed. After a few hours the fluid is found full of stellate needles, which should be collected on a filter, washed with water, and pressed.

It is not needful, however, to use crystallised bile in the first instance; the acid may be thrown down from bile purified according to Theyer and Schlosser's method,‡ and the precipitate thrown into æther forms a heap of stellate crystals.§

Another way is to precipitate a solution of crystallised bile with neutral acetate of lead. After complete precipitation with this salt, a second precipitation may be made with basic acetate of lead to throw down

* Dalton, *New York Medical Journal*, 1874, Vol. xix. p. 589.

† Bogomoloff, *Centralblatt f. d. med. Wiss.* 1869, p. 484.

‡ Theyer and Schlosser, *Annalen d. Chemie und Pharmacie*, 1843, Bd. xlviii. p. 77.

§ Adolph Strecker, *ibid.* 1848, Bd. lxxv. p. 9.

taurocholate of lead. The precipitates are the lead salts of the two bile acids, glycocholic and taurocholic acid. The precipitates must be dissolved in hot alcohol, sulphuretted hydrogen passed through, and then water added to the concentrated alcoholic solution, which throws down the glycocholic acid.

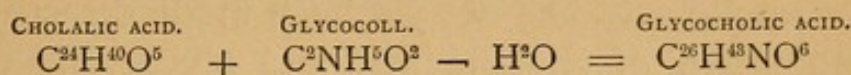
Gorup-Besanez evaporates ox-gall almost to dryness in a water bath, and then extracts with alcohol of 90. *per cent.* The alcohol is distilled or driven off from the filtered solution, the residue is diluted with water and milk of lime is added, to throw down the pigment which combines with the lime. The somewhat yellow coloured filtrate is now first neutralised with sulphuric acid, and then just enough added to throw down the glycocholic acid, but all excess should be avoided. In a few hours the whole becomes a mass of crystals which must be filtered, washed, and pressed.*

A quicker way of preparing pure glycocholic acid is recommended by Hüfner. Fresh ox bile is put into a narrow cylindrical glass and æther poured on to the surface of the bile; then a strong mineral acid is added to the bile so as to throw down the bile acids. First a milky precipitate is formed which later on becomes crystalline, sometimes so rapidly that the whole mass becomes solid; the æther turns of a yellow or brown colour, but after standing some time becomes purple or violet. The mass of crystals must be separated from the æther and shaken up forcibly in a stoppered vessel, then put into a filter and washed on the filter with cold water until the filtrate cease to be of a green colour. This filtrate contains the taurocholic acid which is readily soluble in water. The glycocholic acid is not soluble in cold, but readily in hot, water: to purify the mass on the filter it must be dissolved

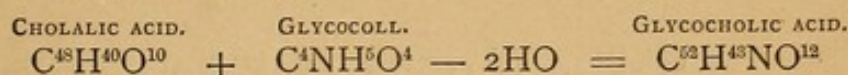
* Gorup-Besanez, *Annalen der Chemie und Pharm.* 1871, Bd. clvii. p. 286.

in boiling water, rapidly filtered, and when cold the acid crystallises out in purity.*

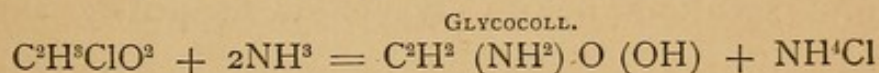
Our knowledge of the composition of glycocholic acid is entirely due to the labours of Strecker. He found that if glycocholic acid be boiled for many hours, about 24, with caustic baryta, that the glycocholic acid is completely decomposed into two bodies: cholalic acid and glycocoll:†



or in the old notation:



A like decomposition takes place if glycocholic acid be boiled with acids, especially hydrochloric acid: a precipitate is thrown down consisting of hydrochlorate of glycocoll, (glycin or glycocine). If this body be dissolved in water, and heated with oxyde of lead, the chloride of lead separated, and the superabundant lead removed with sulphuretted hydrogen, the filtrate may be evaporated for crystallisation. Glycocoll is a crystalline body; it forms large rhombohedra which are easily soluble in water, very little in hot alcohol, insoluble in cold alcohol and in æther. It is not needful to go deeply into the chemistry of this body in this work; but it is well to say that it is an amide uniting with both acids and bases: according to its composition it would be amido-acetic acid. It has been synthetically made by Perkin and Duppa from mono-brom-acetic acid,‡ and by Cahours§ from mono-chlor-acetic acid:



* Hüfner, *Journal f. prakt. Chemie*, 1874, Bd. cxviii. p. 267.

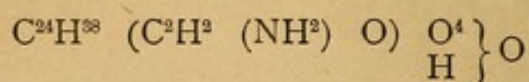
† Adolph Strecker, *Annalen d. Chemie und Pharmacie*, 1848, Bd. lxxvii. pp. 2 et seq.

‡ Perkin and Duppa, *Phil. Mag.* 1857, Vol. xiv. p. 217.

§ Cahours, *Comptes rendus*, 1858, t. xlv. p. 1044.

It may be prepared from gluten, and even in small amount from albuminous bodies. It is important to the physiological chemist because it enters into the composition of hippuric acid as well as of the bile acids. Hippuric acid is benzoic acid *plus* glycoll. Hoppe-Seyler recommends glycoll to be prepared by boiling hydrochloric acid with hippuric acid.* It has no influence on polarised light.

Glycocholic acid has not yet been made directly from a combination of cholalic acid and glycoll. Glycocholic acid may be looked upon as a chol-amide acetic acid:



The crystals of glycocholic acid are fine white needles, which even when looked at with a microscope magnifying 300 times, scarcely show a diameter.

Glycocholic acid is but slightly soluble in water; 1000 parts of cold water dissolve 3.3 of the acid; and the same parts of boiling water 8.3. The solution is sweet and somewhat bitter to the taste; it reddens litmus and shows no reaction with acids, acetate of lead, corrosive sublimate, or nitrate of silver; sub-acetate of lead causes a slight precipitate.

The acid is very soluble in alcohol; and if it be heated in a water bath becomes a syrupy, later on, a resinous mass, from which crystals cannot again be obtained.

In æther, glycocholic acid is but slightly soluble; but much æther must be added to a concentrated alcoholic solution before it be even partly thrown down.

Concentrated sulphuric, hydrochloric, and acetic acids dissolve glycocholic acid. Alkalies readily dis-

* Hoppe-Seyler, *Handb. d. phys. und path. chem. Analyse*, Berlin, 1865, p. 124.

solve it. It expels the carbonic acid from the alkaline carbonates.

The combination of glycocholic acid with soda is that which is the most important, inasmuch as this is the salt which is found in the bile. It crystallises in white needles, just like crystallised bile. It is very soluble in water, less so in absolute alcohol. 1000 parts of alcohol dissolve at 15° C. 39 parts of glycocholate of soda.

There are also glycocholates of potash, ammonia, and baryta, all soluble in water.

De l'Arbre finds that the bile acids unite and form crystals with alkaloids, such as strychnine, brucine, morphia,* &c.

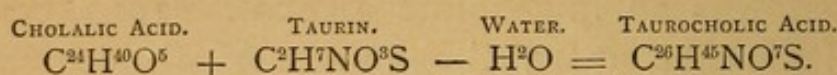
Hoppe-Seyler has found that the bile acids and their derivatives have a marked influence on polarised light. Glycocholic acid has a dextro-rotatory power for red light of $+27^{\circ} \cdot 22$: for yellow light $+29^{\circ} \cdot 93$; and it is inferred for sun light $+36^{\circ} \cdot 15$. The rotatory action is the same whether the acid be in combination with a base or not.†

Taurocholic Acid.—Strecker showed that the precipitate thrown down by sub-acetate of lead, after the precipitate thrown down by acetate of lead had been separated, contained an acid different from glycocholic, inasmuch as sulphur, as well as nitrogen, entered into its composition. He was, however, unable to separate the glycocholate of lead from the taurocholate; he therefore subjected the lead precipitate to the same process, boiling with baryta, that was so fruitful in the decomposition of glycocholic acid. A like decomposition did indeed set in; with cholalic acid, two bodies,

* De l'Arbre, *Chem. Centralblatt*, 1872, p. 231. See also Malinin, *Centralblatt f. d. med. Wiss.* 1868, p. 370.

† Hoppe-Seyler, *Arch. f. path. Anat.* 1858, Bd. xv. p. 130. More elaborate observations by Hoppe-Seyler on this same subject will be found in the *Journal f. prakt. Chemie*, 1863, Bd. lxxxix. p. 257.

taurin and glycocoll, were formed, instead of one, glycocoll. These two were readily separated by means of alcohol containing hydrochloric acid, in which glycocoll is readily soluble, while taurin is but very slightly taken up by it.* Taurocholic acid is therefore a compound of taurin and cholalic acid:



or in the old notation:



Of taurin it will be enough to say that its formula was first accurately given by Redtenbacher,† and a rational formula by Kolbe.‡ It is amido-isæthionic (æthyl sulphuric) acid. It may be formed synthetically by heating the ammoniacal salt of isæthionic acid to $210^{\circ} C.$ § or else by the action of ammonia upon the chloræthyl sulphate of silver.

Taurin is a crystalline body, forming colourless prisms, quadrate, or oftener hexagonal, with four-sided pyramids at each end. Its solution is neutral and it unites with neither acids nor bases. This body is one of the richest in sulphur of those found in the œconomy. It has no action on polarised light.||

Taurocholic acid may be obtained by decomposing its lead salt with sulphuretted hydrogen, filtering, and evaporating at a low temperature. It has not yet been seen in crystals;¶ it is, reversing the property of glycocholic acid, readily soluble in water. The solution is acid and soon decomposes, even on boiling. By

* Strecker, *Annalen d. Chemie u. Pharmacie*, 1848, Bd. lxxvii. p. 31.

† Redtenbacher, *ibid.* 1846, Bd. lvii. p. 170.

‡ Kolbe, *ibid.* 1859, Bd. cxii. p. 241, and 1862, Bd. cxxii. p. 33.

§ Strecker, *ibid.* 1854, Bd. xci. p. 101.

|| Hoppe-Seyler, *Arch. f. path. Anat.* 1858, Bd. xv. p. 132.

¶ J. Parke, Hoppe-Seyler's *Med. chem. Untersuchungen*, Berlin, 1866, p. 160.

boiling with acids or alkalies it is decomposed into taurin and cholic acid.

Strecker describes the alkaline salts of taurocholic acid as very soluble in water and spirit, but insoluble in æther. They have no action on litmus paper. Exposed to moist air, they increase considerably in weight but do not deliquesce. When heated upon platinum foil, the salt first melts, then throws off bubbles, and burns, leaving behind it an ash. The watery solution tastes sweet with a bitter after-taste. The acid is not thrown down by acids, even by concentrated sulphuric acid. If boiled with acids, oily drops of cholic acid are thrown down, and the fluid retains taurin in solution. By adding concentrated solution of potash to a watery solution of an alkaline taurocholate, the potash takes over completely the taurocholate to itself. In the same way the taurocholate drives out the carbonic acid of an alkaline carbonate; but has no influence on a sulphate or chloride. Carbonic acid does not unite with the alkali of any alkaline taurocholate in alcoholic solution. With lime, baryta, and magnesia salts there is no precipitate, nor even with ammonia. With neutral acetate of lead there is no precipitate, but white flakes are thrown down by the sub-acetate. These are dissolved by heat, and again thrown down by cooling, and are also soluble in a great excess of sub-acetate of lead. After complete precipitation with sub-acetate of lead, there appears a fresh precipitate with ammonia.

The watery and alcoholic solutions of taurocholates may be evaporated in a water bath without undergoing change; nor are they, if pure, decomposed by long keeping. The solution of the free acid cannot be evaporated to dryness without decomposition.

In watery solutions of alkaline taurocholates there is no precipitate with acetate of copper, but a little

ammonia throws down bluish white flakes soluble in excess: nitrate of silver gives no precipitate, even with ammonia, and on boiling, a part of the silver is reduced. Perchloride of iron at first gives a precipitate soluble in excess. Perchloride of mercury gives no precipitate, but the nitrate of mercury and chloride of zinc throw down white flakes. Taurocholates give Pettenkofer's reaction.*

Hoppe-Seyler has found that the dextro-rotatory power of taurocholic acid for red light is $+24^{\circ} \cdot 92$; for yellow $+25^{\circ} \cdot 28$.†

The bile acids are not the same throughout the vertebrate sub-kingdom. The bile of the lower animals has been investigated by several chemists, chiefly by Strecker. It would seem probable that the nitrogenous bases of the bile acids are always the same, glycocoll and taurin, while the acid with which they are combined is the body which varies.

Strecker finds the bile acid of dogs to be entirely taurocholic without a trace of glycocholic:‡ but Dr. George Scott found a glycocholate in the bile of a dog, sometimes as much as one-third of the whole bile acid salts.§ Hoppe-Seyler endorses Strecker's statement,|| which appears to be generally received.

Thenard says of the bile of the pig, that, unlike the bile of the ox, it is a true soap: from it he could obtain no picromel.¶

Strecker and Gundelach found in the bile of pigs, as its chief constituent, an acid nitrogenous but free from

* Strecker, *Annalen d. Chemie und Pharmacie*, 1848, Bd. lxxvii. p. 46.

† Hoppe-Seyler, *Arch. f. path. Anat.* 1858, Bd. xv. p. 132.

‡ Strecker, *Annalen d. Chemie u. Pharmacie*, 1849, Bd. lxx. p. 178.

§ George Scott, *Beale's Archives of Medicine*, 1859, vol. i. p. 217.

|| Hoppe-Seyler, *Phys. Chemie*, Berlin, 1878, p. 289.

¶ Thenard, *Mémoires de physique et de chimie de la Société d'Arcueil*, 1807, t. i. p. 49.

sulphur, which they called hyocholic acid.* It differs greatly from the glycocholic acid of oxen. It is insoluble in water, and forms with lime and baryta a salt either insoluble or hardly soluble in water. The alkaline salts are thrown down out of their watery solution by chloride of sodium, chloride of ammonium, or alkaline sulphates, a means by which the acid may be had in purity: the formula for the salts is $C^{54}H^{43}NO^{10} + MO$; for the acid $C^{54}H^{43}NHO^{10}$. The acids make up 75 *per cent.* of the solids of pig's bile; and of this about 0.47 *per cent.* is sulphur. There is, therefore, probably a bile acid which has the same relation to hyocholic acid, as taurocholic has to glycocholic.†

Hoppe-Seyler thinks that the acids of pig's bile have probably a more complicated composition than the glycocholic and taurocholic acid of other mammals, as he finds they have considerable differences in their influence on the polarised beam, differences which are not always constant. Hoppe-Seyler gives $+ 2^\circ$ for hyoglycocholic acid in yellow light, and $+ 23.62^\circ$ for hyocholoidic acid, an acid formed by the boiling of hyoglycocholic acid with hydrochloric acid.‡

The bile of a female kangaroo (*Halmaturus*), was found by Schlossberger to be neutral, and to give a well-marked Pettenkofer's reaction: there were 14.13 *per cent.* of solids, distributed as follows:

Mucus and Colouring Matters	4.34.
Cholestearin and Fat	1.09.
Bile Acid Salts	7.59.
Loss and other Salts	1.11.

Very little sulphur (2.47 *per cent.*) was found, so that the bile of the kangaroo is one of the poorest in tauro-

* Strecker and Gundelach, *Annalen d. Chemie und Pharmacie*, 1847, Bd. lxii. p. 205.

† Strecker, *ibid.* 1849, Bd. lxx. p. 179.

‡ Hoppe-Seyler, *Arch. f. path. Anat.* 1858, Bd. xv. p. 139.

cholic acid yet examined. The bile of the pig, however, contains less sulphur.*

Tiedemann and Gmelin are said to be the first who investigated the bile of geese, though from the imperfect state of the chemistry of the bile at that time but little was added to knowledge by their observations.† Marsson later on took up the work, and found that the bile in the gall bladders of geese fed on oats contained about 20 *per cent.* of solid matter. He found sulphur very abundant in this bile; and thought that it might turn out to contain a new acid, nearly allied to Strecker's choleic acid, and to this new acid he gave the provisional name of chenocholeic acid. It gives Pettenkofer's reaction.‡

Heintz and Wislicenus found a peculiar acid, as Marsson did, in the bile of geese, but they carried their investigations far wider. They found the cholalic acid to be in no way like the ordinary cholalic acid of oxen, or the hyocholalic acid of pigs. Even the shape of the crystals of the soda salt is different. The amount of carbon is much greater, that of oxygen much less, than in the ordinary bile acid, but its formula is homologous with that of hyocholalic acid; the formula of chenocholalic acid is $C^{54}H^{44}O^8$ while that of hyocholalic acid is $C^{50}H^{40}O^8$.

In the bile of geese these observers have also found another acid, containing sulphur, analogous to taurocholic acid, and which they call tauro-chenocholic acid, as in it chenocholalic acid is combined with taurin. Its formula is $C^{58}H^{49}NS^2O^{12}$.§

Berzelius seems to have been the first to examine

* Schlossberger, *Annalen d. Chemie u. Pharm.* 1859, Bd. cx. p. 244.

† Tiedemann and Gmelin, *Die Verdauung*, Heidelberg and Leipzig, 1827, Bd. ii. p. 145.

‡ T. Marsson, *The Chemist*, 1849-50, vol. i. new series, p. 64, abstract from *Arch. der Pharmacie*, 2. Reihe, Bd. lviii. p. 138.

§ Heintz and Wislicenus, *Poggendorff's Annalen d. Phys. und Chemie*, 1859, Bd. cviii. p. 547.

the bile of snakes, of a *coluber* and a *python* ;* though the results of his observations are not now-a-days of any value to the physiologist. Later on Schlieper examined the bile from the gall bladder of a *Boa annaconda*, and found the ashes after examination to consist chiefly of sulphate of soda, and that the dry residue of the bile held about 6 *per cent.* of sulphur.† Schlossberger, in the bile of a *python tigris*, found the same percentage of sulphur, and concludes that in this kind of snake the only bile acid present is the taurocholic in combination with soda.‡

In the bile of salt-water fish there is seen an exception to the general rule that the bile acids are in combination with soda. Strecker found the acid to be chiefly taurocholic, with very small traces, if any, of glycocholic acid. In the bile of the cod (*Gadus morrhua*) and of the turbot (*Pleuronectes maximus* or *Rhombus maximus*) the chief constituent was taurocholate of potash, while the bile of fresh water fish, such as the pike (*Esox lucius*) and the perch (*Perca fluviatilis*) held much more soda, combined in the bile of the pike with glycocholic acid.§

The bile of a species of *Silurus*, taken from a specimen weighing 90 pounds, Schlossberger found neutral and showing a few epithelium cells. It contained 5.52 *per cent.* of solids, composed of 3.63 of bile acid salts, .23 of fat and 1.48 of mucus and pigment. The salts contained a large amount of sulphur; so that in this case also the bile acid was inferred to be chiefly taurocholic, with a small amount of glycocholic acid.||

Scherer found in the bile of a sturgeon both glyco-

* Berzelius, Poggendorff's *Annalen d. Physik und Chemie*, 1830, Bd. xviii. p. 87.

† Schlieper, *Annalen d. Chemie und Pharmacie*, 1846, Bd. lx. p. 109.

‡ Schlossberger, *ibid.* 1857, Bd. cii. p. 91.

§ Strecker, *ibid.* 1849, Bd. lxx. p. 169.

|| Schlossberger, *ibid.* 1858, Bd. cviii. p. 66.

cholic and taurocholic acids.* It gave a well-marked Pettenkofer's reaction.

The bile contains but very little sulphur as sulphuric acid; and so the amount of sulphur present becomes a means for very nearly estimating the amount of taurocholic acid. Advantage has been taken of this by several chemists in analysing the bile; but unfortunately the later-made experiments vary much from those that are earlier. For example, A. Bensch has found the following amounts of sulphur in the bile of different animals:†

	IN 100 PARTS.	
Oxen.	3.39	— 3.78.
Calf, (before weaning). .	4.88.	
Sheep.	5.71.	
Goat.	5.20.	
Pig, (3 analyses) . . .	0.30.	0.32. 0.36.
Bear.	5.75.	
Dog.	6.21.	
Wolf.	5.03.	
Fox.	5.96.	
Domestic Fowl.	4.96.	
Fish of different kinds . .	5.52.	5.58.

It has just been said that Schlieper and Schlossberger found 6 *per cent.* of sulphur in the bile of a *boa* and *python* respectively, and that Scherer and Schlossberger found the bile acids of fish to be almost entirely made up of taurocholic acid.

Külz, on the other hand, using Carius' method of estimating the sulphur, finds as follows:‡

	PER CENT.
Bile of Sheep189.
„ Man136.
„ Swine125.
„ Calves125.
„ Oxen100.

* Scherer, *Verhandlungen d. phys.-med. Gesellschaft in Würzburg*, 1857, Bd. vii. p. 269.

† Bensch, *Annalen d. Chemie u. Pharm.* 1848, Bd. lxxv. p. 194.

‡ Külz, *Arch. f. Anat. Phys. u. s. w.* 1872, p. 106.

Salkowski very properly criticises these results.* A very small amount of bile was used for each analysis, a few milligrammes of sulphates only being obtained; and in this way a large error may creep in if the results be multiplied.

Kunkel also gives .1 grm. in 100 C.C. of bile as the average for a dog.†

DERIVATIVES OF THE BILE ACIDS.

Cholalic acid, as described above, is a product of the decomposition of both glycocholic and taurocholic acid. It is the non-nitrogenous acid which is common to both, and, by combining with the glycocoll and taurin, forms the special acids of the bile.

Cholalic acid is formed by the decomposition of the bile acids by acids, alkalies, or fermentation. Strecker made it by long boiling of the bile acid salts with baryta. The solution, when allowed to cool, gives a crystalline mixture of hydrate of baryta and cholalate of baryta. This is thrown on a filter, washed with a little boiling water, and then thrown into water acidulated with hydrochloric acid. The cholalic acid separates as a resinous body, and the solution only holds chloride of barium. The fluid, from which the cholalate of baryta was filtered off, is mixed with the washings, and carbonic acid passed through, by means of which the baryta is precipitated as far as may be. The fluid is then heated to boiling, filtered from the carbonate of baryta, and the cholalic acid set free from the baryta by means of hydrochloric acid. A small part of the cholalic acid remains in the carbonate of baryta and may be got by treating it with carbonate of ammonia, and then expelling the cholalic acid with a stronger acid. The cholalic acid is thus obtained in three different fluids. This is

* Salkowski, *Centralblatt f. d. med. Wiss.* 1872. p. 885.

† Kunkel, *Arch. f. d. ges. Phys.* 1877, Bd. xiv. p. 345.

the method recommended by Strecker.* Hoppe-Seyler says that the bile should be boiled for 12 or 24 hours with strong potash solution, or baryta solution saturated when hot. The solution should be thrown down with hydrochloric acid, washed with water, dissolved in a little alkali-solution, æther added, precipitated afresh with hydrochloric acid, and then allowed to stand for several days. By the addition of æther the cholalic acid is obtained in crystals. The æther is poured off, the mass pressed, dissolved in hot alcohol, a little water added so that a slight opalescence takes place, and the whole allowed to cool. The cholalic acid forms in tetraëdral crystals,† or, according to Strecker, rarely in quadrate-octaëdra. They are colourless, shining, easily broken. They have a somewhat bitter taste, with a scarcely noticeable sweet after-taste.‡ They need 750 parts of boiling, and 4000 of cold, water for solution. They are readily soluble in boiling alcohol, but on cooling separate out. 1000 parts of cold alcohol of 70 *per cent.* keep 48 parts dissolved. Hoppe-Seyler says the crystals are hardly soluble in æther; Strecker that one is soluble in 27 parts of æther.

The amorphous variety, according to Hoppe-Seyler, is like wax and may be kneaded. It is somewhat soluble in water, somewhat more in æther, and very soluble in alcohol.

The formula for cholalic acid is $C^{24}H^{40}O^5$. Its rational formula is unknown. The crystals from æther contain 2 molecules of water, those from alcohol 5.

Cholalic acid combines readily with alkalies and drives out carbonic acid from its combination with them. The alkaline salts are all soluble in water: the baryta and

* Strecker, *Annalen d. Chemie und Pharm.* 1848, Bd. lxxvii. p. 3.

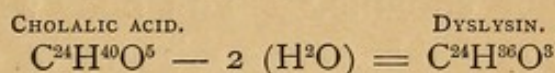
† Hoppe-Seyler, *Handb. d. phys. u. path. chem. Analyse*, Berlin, 1865, p. 90.

‡ Trifanovsky, (*Arch. f. d. g. Phys.* 1874, Bd. ix. p. 495) says cholalic acid has an intensely bitter taste without any sweet after taste.

lime-salts are with trouble soluble in cold water, but more easily in hot, are very soluble in alcohol. They form fine needles, often stellate. The cholalates of lead and silver are insoluble in water, but soluble in hot alcohol.

Cholalic acid gives Pettenkofer's reaction; it has a dextro-rotatory action on polarised light: $+24^{\circ}55$ for red, and $+27^{\circ}66$ for yellow, light.* It dissolves the red blood corpuscles.†

Dyslysin, a body noted and named by Berzelius,‡ is formed by heating cholalic acid to 190° or 200° C. when the acid is split up into dyslysin and water:



By boiling with potash, dyslysin takes up water and becomes again cholalic acid. The same decomposition takes place on boiling cholalic acid with acids. A mucilaginous body of a brown colour is separated. This is insoluble in water and cold alcohol; slightly soluble in hot alcohol, soluble in æther. It is not taken up by ammonia or potash; by boiling with alcoholic potash or fusing with potash it is dissolved, and on adding acids a body is thrown down which is no longer dyslysin but choloidic acid.

Choloidic acid, a body first named by Demarçay,§ has been further investigated by Strecker.|| At ordinary temperatures it is firm and white, often, however, somewhat coloured. It fuses in boiling water without being dissolved. When dry it fuses at over 150° C.

* Hoppe-Seyler, *Arch. f. path. Anat.* 1858, Bd. xv. p. 138.

† Idem, *ibid.* 1862, Bd. xxv. p. 183. Baumstark has published some interesting observations on cholalic acid. (*Berichte d. deutschen chem. Gesellschaft zu Berlin*, 1873, Bd. vi. p. 1185.)

‡ Berzelius, (*Annalen d. Chemie u. Pharm.* 1840, Bd. xxxiii. p. 147), calls it thus from its difficult solubility: *δυσ* and *λύσις*.

§ Demarçay, *Annales de chimie et de physique*, 1838, t. lxvii. p. 198.

|| Strecker, *Annalen d. Chemie und Pharm.* 1848, Bd. lxvii. p. 22.

The alcoholic solution is made opalescent by water and is acid to litmus. In æther it is only slightly soluble. It is best purified by solution in alcohol and precipitation by æther. It combines with bases and drives out carbonic acid by the aid of heat. The salts of choloidic acid are soluble in water and alcohol, but insoluble in æther.

The weakest acids drive out choloidic acid, even a stream of carbonic acid. The taste is purely bitter, without any sweet after-taste. The formula which Strecker gives is $C^{48}H^{39}O^9$, on the old system.

Hoppe-Seyler, however, doubts if this choloidic acid be anything but cholalic.* The body which Strecker analysed was probably only a mixture of cholalic acid, dyslysin, and cholonic acid. Like cholalic acid, the body obtained by Strecker's process crystallises in octaëdra and tetraëdra; and the crystals by drying lose 10.2 *per cent.* of water. The formula, after Gerhardt, is $C^{24}H^{40}O^5 + 2\frac{1}{2} H^2O$, which equals 9.93 *per cent.* of water. It has much the same action on polarised light as cholalic acid.

Cholalic acid	in alcoholic solution =	+ 35°.2.
Acid prepared from dyslysin	„ „	= + 35°.4.
Cholalate of potash	„ „	= + 31°.4.
Salt of potash from dyslysin	„ „	= + 30°.8.

The baryta salt is insoluble in water and thus is distinguished from glycocholic and cholalic acid. Baumstark, on the other hand, believes that a distinct choloidic acid does exist.†

Cholonic acid is a nitrogenous derivative from glycocholic acid. If glycocholic acid be added to strong sulphuric acid, the glycocholic acid is dissolved; but if the mixture be warmed, cholonic acid separates, as an

* Hoppe-Seyler, *Journal f. pract. Chemie*, 1863, Bd. lxxxix. p. 83.

† Baumstark, *Berichte der deutschen chem. Gesellschaft zu Berlin*, 1873, Bd. vi. p. 1187.

amorphous precipitate, which is not soluble in water but is soluble in alcohol. It is not crystallisable. This acid is also formed with cholalic acid when glycocholic acid is boiled with hydrochloric acid. Its formula is $C^{26}H^{41}NO^5$. The dextro-rotatory action of cholonic acid is the same as that of glycocholic acid.

Parke did not succeed in getting from taurocholic acid an acid analogous to the cholonic acid derived from glycocholic acid.*

* J. Parke, Hoppe-Seyler's *Med. Chem. Untersuchungen*, Berlin, 1866, p. 161.

CHAPTER II.

THE BILE PIGMENTS.

THE biliary pigments seem to have been first studied by the illustrious Berzelius,* afterwards by Scherer,† Hein,‡ and Heintz.§ Städeler and Maly have paid special attention to these colouring matters.

The name cholepyrrhin is commonly said to have been given by Berzelius to the orange red pigment of the bile. F. Simon invented a barbarous word, biliphæin,|| compounded of Greek and Latin, the use of which has been unfortunately endorsed by Heintz. Dr. Thudichum uses the word cholophæin,¶ to avoid this bastard word. Städeler called this pigment bilirubin, forming the word with a cognomen like the other names which Berzelius used; biliverdin, bilifulvin, and the like.** Maly has continued the use of the name cholepyrrhin.†† The name bilirubin is so convenient and so commonly used that I shall adopt it in the following pages.

The colouring matters of the bile do not seem to give any absorption bands in the spectrum; as Thudichum,‡‡

* Berzelius, *Annalen d. Chemie u. Pharm.*, 1840, Bd. xxxiii. p. 139.

† Scherer, *ibid.* 1845, Bd. liii. p. 377.

‡ Hein, *Journal f. pract. Chemie*, 1847, bd. xl. p. 47.

§ Heintz, Poggendorff's *Annalen d. Physik u. Chemie*, 1851, bd. lxxxiv. p. 106.

|| Simon, (*Animal Chemistry*, 1845, Sydenham Soc. Edition vol. i. p. 43,) says that cholepyrrhin was first used by Berzelius, and biliphæin by Simon.

¶ Thudichum, *Tenth Report of the Medical Officer of the Privy Council*, London, 1868, p. 243.

** Städeler, *Annalen d. Chemie u. Pharm.* 1864, Bd. cxxxii. p. 323.

†† Maly's observations will be found in the publications named below: *Sitzungsberichte d. math.-naturw. Classe d. k. Akademie der Wissenschaften*, Wien 1868, Bd. lvii. Abth. ii. p. 97. *Ibid.* 1869, Bd. lix. Abth. ii. p. 597. *Ibid.* Jahrg. 1874, Bd. lxx. Abth. iii. p. 72: also in *Annalen der Chemie und Pharmacie*, 1872, Bd. clxiii. p. 77. *Ibid.* 1876, Bd. clxxxi. p. 106.

‡‡ Thudichum, *op. cit.* p. 251.

Preyer,* and Vierordt† agree. It is only when they are subjected to oxydising agents that these bands make their appearance. Maly noted that a solution of bilirubin in chloroform removed the blue and violet out of the spectrum up to 70; and that even very dilute solutions removed the violet end of the spectrum. Biliverdin in alcoholic solution removed both ends of the spectrum.‡ Dr. Dalton has described§ an extreme shortness of the bile spectrum with a band, which he thinks characteristic, at C. This band is best seen in bile which has a distinct green colour; it is not so well seen if the bile be brown or yellow; if bile lose its green colour, the band disappears, but is restored if the green colour be brought back by adding iodine. Dr. Dalton thinks this band to be due probably to the presence of biliverdin. Another band or two may sometimes be seen at D or D 30 E, but never so distinctly as the band at C.

Cholepyrrhin, bilifulvin, or bilirubin, has not been studied much as a product direct from the bile, but as a constituent of gall stones from men or oxen in which it appears in combination with calcium. Maly recommends the gall stones to be broken up, boiled with alcohol and filtered hot. The brown residue on the filter is washed with æther and digested with acetic acid. The acid solution is filtered, and the residue washed with water and alcohol. The remaining powder is now dried and digested for several days in chloroform at the ordinary temperature, or for a few hours in a water bath. The chloroform takes up the pigment, and the bilirubin is obtained by distilling off the chloroform, and washing

* Preyer, *Die Blutkrystalle*, Jena 1871, p. 187.

† Vierordt, *Zeitschrift f. Biologie*, 1874, Bd. x. pp. 44 and 48.

‡ Maly, *Sitzungsberichte d. math.-naturw. Classe d. k. Akad. der Wissenschaften*, Wien, 1868, Bd. lvii. Abth. ii. p. 106.

§ Dalton, *New York Med. Journal*, 1874, vol. xix. p. 579.

with spirit. If the pigment be wished for very pure, the whole process had better be repeated once or twice.*

Städeler recommends another process. The gall stones are digested in æther, and the residue extracted with hot water, dried, and then treated with chloroform. This gives an impure solution of bilirubin. It must be evaporated to dryness and then treated with hydrochloric acid. Carbonic acid is given off, and the violet filtrate contains a great quantity of lime and magnesia. The residue on the filter must be washed and dried, and is then of a dark brown green. To purify it, the bilirubin must be dissolved several times in chloroform, the filtrate evaporated, and the residue washed with æther and spirit. The washings with alcohol are always more or less green, while the bilirubin remains on the filter as an orange-red granular-crystalline powder.

Dr. Thudichum recommends a long and troublesome process. Gall stones from the ox are powdered and made into a dough with a little hot water; an excess of hot water added and the whole well stirred. After standing for several days the fluid is separated by decantation, a process frequently repeated. At last the whole is thrown upon a filter, and the paste left is put into a flask with a large quantity of spirit and boiled. After exhausting the powder with alcohol, it is treated for several days with cold dilute hydrochloric acid. The powder is washed by decantation, lastly on the filter, and a second time with alcohol. After this the powder may be washed with æther, but if the foregoing operations have been properly performed, this last process will be unnecessary. When dried, the powder is boiled with pure chloroform, and exhausted with this liquid. The filtered solution is evaporated, and the residue with absolute alcohol till the latter be nearly colourless, and the residue on the filter red without any admixture of green.†

* Maly, *op. cit.* p. 96.

† Thudichum, *op. cit.* p. 241.

Heintz appears to be the first who gave a distinct formula for bilirubin.* Scherer and Hein made elementary analyses, but did not succeed in composing a distinct formula. According to Heintz the formula is $C^{31}H^{18}N^2O^9$. Städeler and Maly, however, both give $C^{32}H^{18}N^2O^6$ or in the new notation $C^{16}H^{18}N^2O^3$, and this appears to be generally accepted. Maly believes that bilirubin is the amide of biliverdin which possesses the properties of an acid in uniting with bases.† Dr. Thudichum, however, denies this, and asserts the formula to be $C^9H^9NO^2$.‡

Dr. Thudichum describes two modifications of the red colouring matter of the bile; the one, amorphous, of a bright red colour, which he calls bilirubin; the other, crystalline, of a purple-brown colour, which he calls biliphæin or cholophæin. He regards them as identical chemical substances. The crystals belonged to the rhombic system, "being prisms in some crystallizations, simple, and with nearly obtuse right angles, in others with sharp angles on the one, obtuse angles on the next edge, and planes from secondary prisms cutting off the sharp angles of the primary ones."

Bilirubin heated on platinum foil leaves no residue behind.

Städeler says that amorphous bilirubin is orange coloured; the crystals show the dark red of chromic acid. He finds that good crystals can rarely be got from the solution in chloroform; better are had direct from the bile. Maly describes them as doubly convex, like the section of a biconvex lens.

In water, bilirubin appears to be quite insoluble, slightly in æther, and a little more in spirit. The alcoholic solution made while hot is golden yellow, when

* Heintz, *op. cit.* p. 114.

† Maly, *Centralblatt f. d. med. Wiss.* 1864, p. 640.

‡ Thudichum, *op. cit.* pp. 241 and 244.

cold it becomes brighter, and if filtered the greater part of the pigment adheres to the paper so that the filtrate shows only a slight degree of yellowness. Chloroform dissolves bilirubin even in the cold; the more crystalline the bilirubin, the slower the solution. The chloroform acquires a yellow or pale orange colour. A saturated solution is dark brown red. Sulphide of carbon and benzol are also good solvents, to which Dr. Thudichum agrees, but Maly says that this last only dissolves inconsiderable amounts. This last observer remarks that bilirubin is insoluble in saliva and white of egg; and that solution of soap is only somewhat coloured. In hot amylic alcohol, fatty oils, and glycerine, it is also a little soluble. Städeler says it is soluble in warm turpentine and fatty oils.

Bilirubin is soluble in ammonia and the caustic alkalis, and the solutions are intensely coloured. Städeler found that an alkaline solution of one in 15000 was distinctly orange in a layer 15 millimeters thick; that is, a little over half an inch; a layer of the same thickness, of one in 20,000, was a deep golden yellow; one in 25,000 to 100,000, pure yellow, like solutions of chromate of potash. A yellow colour was still perceptible in solutions of one in 500,000; and in a layer, two inches thick, of a solution of one in a million. A solution of one in 30,000 or 40,000 stained the skin yellow. The value of these observations will be seen when the amount of bilirubin in the urine of jaundice is discussed, and the amount of bilirubin which is secreted by the liver in obstruction to the bile ducts.

The alkaline solution is thrown down by acids. Strong sulphuric acid dissolves bilirubin with a red brown colour, which after a time becomes discoloured and dirty brown green. If the red brown solution be poured into water, dark brown flakes are thrown down which may be readily filtered from the colourless solu-

tion. Maly says that the body remaining on the filter is no longer bilirubin and does not give Gmelin's reaction. This is denied by Städeler, who notes that the red in the play of colours is remarkably fine.

The oxydising action of nitric acid upon bilirubin has long been known as Gmelin's test. Städeler says that a quarter of a milligramme dissolved in 4 C.C. can be readily detected by this means, and that the colours still appear in a solution of one in 70,000 or 80,000. The yellow colour is changed by the action of the acid into green, then blue, violet, ruby red, and lastly dirty yellow. All these stages of oxydation correspond to bodies which can be isolated and preserved. If a solution of bilirubin in chloroform be acted on by a drop or two of nitric acid, and spirit added as soon as the blue or violet colour appears, the solution becomes deep blue and remains so. In the same way a fine green or red can be had, according to the time at which the spirit of wine is added. Heynsius and Campbell have made a special study of the spectra of these bodies.*

The derivatives of the bile pigments cannot be more than mentioned here, as their discussion would in most points be foreign to the object of this work. Their history begins with Städeler, who has the merit of being the first to point out the kindred of the blue product of the oxydation of bilirubin with the indigo colouring matter of the urine.† In 1869 Jaffe named the colouring matter of the urine urobilin, because he believed it to be a derivative of the bile pigment, whether by oxydation or not was left undetermined.‡ Heynsius and Campbell believe it to be due to oxydation;§ Maly, however, to re-

* Heynsius and Campbell, *Arch. f.d. ges. Phys.* 1871, Bd. iv. p. 497.

† Städeler, *op. cit.* p. 333.

‡ Jaffe, *Arch. f. path. Anat.* 1869, Bd. xlvii. p. 423. See also *Arch. f. ges. Phys.* 1868, Bd. i. p. 262. Magendie (*Précis élém. de Phys.* Paris, 1836, 4e éd. t. ii. p. 474, note) conjectures: Il est probable que la matière jaune de la bile est aussi celle qui colore le sérum du sang, l'urine etc.

§ Heynsius and Campbell, *loc. cit.*

duction.* Vanlair and Masius describe another derivative, found in abundance in the fæces, which is closely allied to urobilin, and which they name sterco-bilin.†

The relation of the bile pigments to the colouring matters of the blood is that which has the greatest attraction for the physician, inasmuch as much of the doctrine of hæmatogenous jaundice depends upon the belief that the two bodies are the same. Doubtless the idea that hæmatoidin and bilirubin are identical has much to recommend it to the notice of physiological chemists, but the notion has, I think, been asserted with scarcely sufficient proof. It is, however, an example of the rashness which characterises the present generation of physiological chemists; they make up for the extreme uncertainty of their opinions by an increased boldness of assertion.

Saunders, more than 80 years ago, thought that there might be some relation between the colouring matters of the blood and the bile pigments.‡ Frerichs, in his essay on the chemistry of human bile, makes the short remark that the colouring matters are allied on one side to hæmatin and on the other to black pigment;§ but two years later Virchow, in the midst of his well-known work on the pathological pigments, opened the question of the relation of the bile colouring matter to the blood. Speaking of the red sealing-wax like matter which is so

* Maly, *Annal. d. Chemie. u. Pharm.* 1872, Bd. clxiii. p. 77. He has named the last product of oxydation choletelin, from *τέλος*, end. *Sitzungsbb. d. math.-naturw. Classe d. k. Akad. d. Wiss. Wien*, 1869. Bd. lix. Abth. ii. p. 605.

† Vanlair and Masius, *Centralblatt f. d. med. Wiss.* 1871, p. 369. See also Stokvis, *ibid.* 1872, pp. 3 and 785, and 1873, p. 211; and *Journal of the Chemical Society*, 1872, vol. xxv. p. 308, and 1873, vol. xxvi. pp. 78 and 288. Vierordt, *Zeitschrift f. Biologie*, 1873. Bd. ix. p. 160, and 1874, Bd. x. p. 21.

‡ Saunders, *A Treatise on the Structure, Economy, and Diseases of the Liver*, London, 1803, third edit. p. 147. "Green and bitter bile being in common to all animals with red blood, and found only in such, makes it probable that there is some relative connexion between this fluid and the colouring matter of the blood, by the red particles contributing more especially to its formation." Cf. p. 160.

§ Frerichs, *Hannoversche Annalen*, 1845, Jahrg. v. p. 145.

often found in echinococci cysts in the liver, he says that, in cases where this matter had undoubtedly had its origin in bile, he had found the crystals on the wall of the cyst very like those of old blood clots. Some of these crystals he attempted to examine chemically; but naturally the tests could not be very satisfactorily applied with so small a quantity, and with such impure materials. He found the crystals insoluble in æther, alcohol, or alcohol containing sulphuric acid, or turpentine. No change took place with chlorine vapour, while old *corpora lutea* were completely bleached. Both were acted on by sulphide of ammonium, the crystals remaining unchanged, while the *corpora lutea* became black. With nitric acid they quickly became brown-red, then intensely green, blue, and rose coloured. The crystals were soluble in alkalies. Virchow thinks these observations make it very probable that blood colouring matter may be changed into bile pigment.*

Robin also gave great help to Virchow's notions. A mass, weighing 3 grammes, of the red colouring matter taken from hydatid cysts of the liver, was found to consist entirely of very regular crystals, quite like those described by Virchow. They were completely dissipated by heat and were insoluble in water, alcohol, æther, glycerine, and acetic acid; but soluble in ammonia; nitric acid quickly dissolved the crystals with effervescence, leaving a red solution; sulphuric acid did not dissolve them, but they became greenish. Robin thought the mass had its source in extravasated blood. An elementary analysis gave the following results:

	i.	ii.	iii.
Carbon	65.046.	65.851.	
Hydrogen	6.37.	6.465.	
Nitrogen			10.5050.
Oxygen	18.0888.	17.1788.	
Ashes	00.0002.	00.0002.	

* Virchow, *Arch. f. path. Anat.* 1847, Bd. i. p. 427.

Städeler and Maly give as the percentage of their analyses of bilirubin, the following figures :

	STÄDELER.*	MALY.†
Carbon	67.15.	67.16.
Hydrogen	6.27	6.20.
Nitrogen	9.59.	
Oxygen	16.99.	

The percentage analyses of these two bodies, therefore, correspond in many particulars. Robin compares his analysis with one of Mulder's, of hæmatosin, and appears to think that the substance analysed was a derivative of the blood, without the iron salts. He remarks that the amount of blood extravasated in this cyst must have equalled 1800 grammes at least in order to furnish this quantity, 3 grammes of colouring matter.‡ It is hard to see how so much blood can have been poured into the cyst, but it is easy to understand that a great deal of bile might have found its way into the sac ; it is common to find this red sealing-wax like stuff in cysts communicating with the bile ducts. Virchow's opinion§ that this red matter had its source in the bile would seem to be correct. It is very likely that Robin analysed only an impure bilirubin. Städeler points out that Robin's formula, $C^{14}H^9NO^3$, is not justified by the analysis, but that $C^{30}H^{18}N^2O^6$ would be more correct ; the hydrogen only in this case being .1 and .2 *per cent.* less than found.||

Zenker and Funke say that bilifulvin, that is, bilirubin, either spontaneously or by treatment with æther, changes into fine large crystals which shew "all the properties"

* Städeler, *Annalen d. Chemie u. Pharmacie*, 1864, Bd. cxxxii. p. 328.

† Maly, *Sitzungsberichte der math. wiss. Classe der k. Akad. Wien*, 1868, Bd. lvii. Abth. ii. p. 97.

‡ Robin, *Comptes rendus*, 1855, t. xli. p. 506.

§ Virchow, *loc. cit.*

|| Städeler, *op. cit.* p. 348.

of hæmatoidin, and are therefore identical with it.* It would be, however, interesting to know what "all the properties" of hæmatoidin are.

Jaffe examined an old hæmorrhage into the brain with a view to getting bilifulvin from it. It was dried in a water bath, cut up fine, and extracted with chloroform, after being first moistened with a little alcohol. The extract becoming of a deep yellow colour: the chloroform was then distilled until but a few drops were left, and these were allowed to evaporate spontaneously in a watch-glass. This should be carried on in the dark, in order to hinder oxydation. The crystals left after this evaporation were golden yellow in colour, and remarkably fine; they corresponded closely in shape to those of hæmatoidin. Jaffe, wishing to free them from fat, found a good number of them soluble in æther. The remainder was easily soluble in carbonate of soda. The yellow solution became green during filtration. A small residue was lastly treated under the microscope with nitric acid. The crystals shewed the well-known reaction of bile pigment, becoming first green, then blue. Jaffe had no longer any doubt that by simple recrystallization of hæmatoidin, bilifulvin can be had: therefore that the two bodies are identical. It must be, however, noted, that Jaffe confesses that he was unable to obtain bilifulvin from other old hæmorrhages which had lain long in spirit.†

Hoppe-Seyler found in the fluid from a cyst in the breast, crystals, which from their crystallisation and reaction with nitric acid he judged to be the same as bile pigment, and yet from the source, as in Jaffe's, could not have had their origin in the bile.‡

Valentiner is said to have made some observations

* Funke, *Lehrbuch d. Physiologie*, Leipzig, 1860, 3te Aufl. Bd. i. p. 246.

† Jaffe, *Archiv f. path. Anat.* 1862. Bd. xxiii. p. 192.

‡ Hoppe-Seyler, *ibid.* 1862, Bd. xxiv. p. 10.

which favoured the belief that hæmatoidin and bilirubin are identical, finding crystals of the same shape as hæmatoidin in an extract of bile with chloroform. I have not, however, been able to see the journal* in which the paper was published, so that I can give no trustworthy account of its contents.

Städeler, criticising Valentiner's work, says that he has always found the crystals of bilirubin to be less perfect, as the solution out of which they form approaches purity. If bile be shaken up with chloroform, as in Valentiner's work, and the chloroform allowed to evaporate, there form orange coloured elliptic tables, or very small, almost right angled, tables, the angles of which are very different from those of hæmatoidin.

The results were the same in nearly every case, the rhomboid forms were always recognised, with some slight changes in the sides and angles in which the diagonals of the rhomboids were marked by changes of colour. Only as an exception were seen forms which approached the ordinary hæmatoidin appearance. Städeler also found that the crystals which formed out of benzol and sulphide of carbon solutions showed greater resemblance to hæmatoidin; hæmatoidin has never convex surfaces, while these are commonly seen in bilirubin crystals, so that at first sight they may be mistaken for uric acid.†

The important point, however, is the analysis, and it would seem that an analysis of hæmatoidin has yet to be made. Holm, under Städeler's guidance, and in his laboratory at Zürich, has attempted a further study of the differences between hæmatoidin and bilirubin.‡ He first tried to win from old hæmorrhages in the brain a sufficient amount of

* Valentiner, Günsburg's *Zeitschrift f. klin. Med.* 1858, p. 46.

† Städeler, *op. cit.* p. 344.

‡ Holm, *Journal für praktische Chemie*, 1867, Bd. c. p. 142.

hæmatoidin by means of extraction with chloroform. He found, however, that but very little could be had in this way. He noted, however, as Salkowski has done, that the yellow colour of the chloroform extract changed by exposure to the light into a bright green. The next attempt was on the *corpora lutea* of cows, in these good crystals were rarely met with. The hæmatoidin was extracted by chloroform or sulphide of carbon, from which it could readily be obtained in crystals. The crystals were found to be acute angled triangular tables, of which one side is convex; this convex side can be replaced by two straight lines whereby the tables become somewhat of the shape of a delta. Two of these triangular tables may be joined so as to present the appearance of the ordinary rhombic crystals of hæmatoidin.

It has been said that hæmatoidin is soluble in æther and sulphide of carbon. In absolute æther it is less soluble than in these. It is not soluble in absolute alcohol or water, nor in ammonia or soda. Acetic acid (glacial) dissolves it when warmed, and if to this solution a drop of ordinary nitric acid be added, the mixture becomes blue, but this colour immediately disappears, and the solution remains colourless. The solution of hæmatoidin in chloroform gives no Gmelin's reaction with nitric acid, nor even the blue colour just spoken of: the colour of the yellow solution is simply discharged.

Holm sums up: Bilirubin and hæmatoidin have not only different forms and colours but different chemical properties. The former shows the properties of a weak acid; the latter is indifferent.

Bilirubin is soluble in sulphide of carbon with a golden yellow colour; hæmatoidin with brilliant red.

Bilirubin is insoluble in æther; hæmatoidin soluble.

Bilirubin is readily soluble in alkalies; hæmatoidin insoluble.

Salkowski, however, suffers not this statement of Holm's to go undenied. The contents of a thyroid cyst were obtained by puncture during life. The mass showed all the appearances of bilirubin. Under the microscope good rhombic tables were seen which were readily soluble in chloroform with golden yellow colour, and a little also in æther. Both these solutions readily gave up this body when shaken with a weak soda solution, while the chloroform or æther became colourless. The alkaline solution gave the well-known Gmelin's reaction with nitric acid, and not merely a rapidly disappearing blue, as Holm found with his hæmatoidin solutions. Exposed to the air the solutions became green.

Salkowski confesses, however, that the body which he extracted was so small in amount that it was only enough to make out these foregoing properties.*

Preyer, so well known for his researches on the blood crystals, is very strongly of opinion that bilirubin and hæmatoidin are not identical. He finds the spectrum of the two bodies entirely different. The chloroform extract of gall stones shows in the most dilute, as well as in the most saturated solutions, no absorption bands from A to G. With increased concentration, the refrangible part towards the green gets more and more dark without showing bright intervals.

Now the hæmatoidin extracted by chloroform from the *corpus luteum* of the cow, in which Preyer noted abundance of hæmatoidin crystals, behaved quite differently. The yellow chloroform extract gave a characteristic spectrum; a well-marked absorption band between b and F, close to F, and a smaller one between F and G. If the concentration were increased, an absorp-

* Salkowski, *Medicinisch-Chemische Untersuchungen*, herausgeg. von Hoppe-Seyler, Berlin, 1868. Heft iii. p. 436.

tion band appeared between 80 and 115, while red, orange, yellow, and green remained bright.

Preyer found the same spectrum in hæmatoidin crystals from an old hæmorrhage into the brain; so that it is not another body, taken up from the *corpus luteum* by the chloroform which gives the two bands. Another reason that bilirubin is different from hæmatoidin is the great colouring power of the former, which the latter does not possess. Also in æther containing fat, hæmatoidin is soluble, while bilirubin is not, as Preyer has convinced himself.*

Thudichum, however, asserts that the body which Holm, Preyer, and other observers have examined is not hæmatoidin but lutein; and that lutein differs altogether from bilirubin, or as Thudichum calls it, cholophæin.† The lutein of Thudichum appears to resemble the luteo-hæmatoidin or hæmolutein of Piccolo and Lieben.‡

In conclusion, it may be observed that there are at present scarcely sufficient data for the formation of a trustworthy opinion that bilirubin and hæmatoidin are identical. The shape of the crystals, the presence of iron, the solubility in various reagents, are given differently by different observers.

Kühne§ and Hoppe-Seyler|| boldly cut the knot by using hæmatoidin as a synonym for bilirubin; but if the observations of Preyer on the spectrum of the two bodies be in any way trustworthy, it will hardly be possible to continue this assertion. All observers who have examined the spectrum of bilirubin announce it to be free from absorption bands; but even the hæmatin free

* Preyer, *Die Blutkrystalle*, Jena, 1871, p. 188.

† Thudichum, *Proceedings of the Royal Society of London*, 1869, vol. xvii. p. 255.

‡ Piccolo and Lieben, *Giornale di scienze naturali ed economiche*, Palermo, 1866, vol. ii. p. 258.

§ Kühne, *Lehrb. d. phys. Chemie*. Leipzig, 1866, p. 72.

|| Hoppe-Seyler, *Handb. d. phys. und path. chem. analyse*, Berlin, 1865, p. 161.

from iron shows according to Hoppe-Seyler four absorption bands in the red, yellow, and green.* The balance of evidence is in my opinion against the identity of the two bodies.

Bilirubin enters readily into combination with bases† and these combinations for the most part are insoluble in water, spirit, æther, or chloroform. The best known combination is that with calcium so often met with in gall stones. It may be prepared by decomposing a weak ammoniacal solution of bilirubin with chloride of calcium; the bilirubin-calcium is thrown down as a dark red precipitate. Its formula according to Städeler, who wrote in the præ-Gerhardtian days, is $C^{32}H^{17}CaN^2O^6$: or according to the modern notation $C^{16}H^{17}CaN^2O^3$. According to Maly, bilirubin is the amide of biliverdin which possesses the properties of an acid.‡

Biliverdin. The name biliverdin was first used by Berzelius who thought this green pigment of the bile of herbivorous animals allied to the vegetable chlorophyll.§ Heintz|| first gave it a formula $C^{16}H^9NO^5$; Maly, however, gives a formula $C^{16}H^{18}N^2O^4$ which differs from that above in containing less oxygen.¶ It would appear from this latter that biliverdin is only bilirubin with one atom of oxygen more, as is seen by the following equation, $C^{16}H^{18}N^2O^3 + O = C^{16}H^{18}N^2O^4$. Städeler assumes that bilirubin takes up water as well as oxygen in becoming biliverdin and adds two molecules of water to

* Hoppe Seyler, *Arch. d. path. Anat.* 1864, Bd. xxix. p. 235.

† Thudichum (*Tenth Report &c.* Lond. 1868, p. 244), gives a full account of these.

‡ Maly, *Centralblatt f.d. med. Wiss.* 1864, p. 640.

§ Berzelius, *Annalen d. Chemie*, 1840, Bd. xxxiii. pp. 140 and 177. Biliverdin has been called by Dr. Thudichum cholo-chlorine (*Tenth Report of the Medical Officer of the Privy Council*, 1868, London, p. 249.) This attempt to disturb the old name is to be regretted, as no good object can possibly be attained. See also Thudichum, *Journal of the Chemical Society*, 1876, vol. ii. p. 27.

|| Heintz, Poggendorff's *Annalen d. Physik u. Chemie*, 1857, Bd. lxxxiv. p. 117.

¶ Maly, *op. cit.* 1868, Bd. lvii. Abth. ii. p. 105. See also the same *Sitzungsberichte*, Jahrg. 1874, Wien, 1875, Bd. lxx. Abth. iii. p. 72.

the formula: but this theory is confessedly founded upon the analysis by Heintz of an impure biliverdin, so that in this matter Maly's formula should be received rather than Städeler's.

Dr. Thudichum gives the formula $C^8H^9NO^2$ and thinks that biliverdin arises from bilirubin by the addition of 2 atoms of oxygen and subtraction of one of carbonic acid.

Maly says that there are three sets of reagents by means of which bilirubin can be converted into biliverdin: acids, alkalies, and bromine and iodine.

Maly finds that the action of acetic acid and chloroform upon bilirubin, in sealed tubes, and aided by the heat of a water bath, is to change the bilirubin, into a green body. The change of colour is complete, and no other reaction shows it so well. Other acids, as hydrochloric, heated with bilirubin, cause the formation of a green body. Phipson has recommended the use of strong sulphuric acid for this purpose.* Maly found that anhydrous sulphurous acid did not change bilirubin into biliverdin, when heated in sealed tubes in a water bath: the alcoholic solution remained pure golden yellow. This seemed to show that the oxygen comes from the air, not from the acid, as in presence of sulphurous acid there could scarcely be oxydation of a second body.

Also with alkalies, Maly found that if bilirubin were dissolved in dilute soda solution, and one half put in a tube above mercury, the other left open in a dish to the air, the portion left open to the air became brown green in a few days, while the portion cut off from the air retained its red brown colour at the end of a month. If a few bubbles of oxygen were now allowed to enter the tube with the quicksilver, they were gradually absorbed and the fluid became green.

* Phipson, *Journal of the Chemical Society*, 1867, vol. xx. p. 458.

Another solution of bilirubin in weak soda was poured into a U tube with one end sealed, and the sealed end completely filled with the fluid. Here one end only of the fluid was exposed to the air; and if the green colour were due to oxydation from the air, the colour would first appear at that end which was exposed and gradually spread by the bent part into the closed tube. This was really the case.

In another experiment Maly introduced dry bilirubin into a strong glass tube within which were a few glass globules with thin walls containing dilute soda solution. The glass tube was drawn out into a fine capillary nozzle, bent into a U shape. The glass tube and its contents were now raised by means of a water bath to the temperature of 23.1° C. The capillary tube was then quickly sealed with the blow-pipe. The globules were now broken, and in a few days the fluid became green. The tube was then again heated to 23.1° and the end of the capillary tube broken off under water. Water immediately found its way through the capillary tube into the glass.

These experiments show that the oxygen in the formation of biliverdin is derived from the air. Indigo white, gallic acid, and pyrogallie acid behave in this way just as bilirubin does.*

Besides the acids and alkalies, Maly finds that bromine and iodine have also an action upon bilirubin, bromine especially so. If bilirubin be introduced into a bell jar in which moist air and bromine gas are present, the bilirubin soon becomes dark, and no longer soluble in chloroform, but is soluble in spirit with a pure green colour. The action of the bromine may very easily go too far, so it is better to use the following method: a yellow solution of bilirubin in chloroform is mixed with a few drops of a very weak alcoholic solution of bromine.

* Maly, *Wien. Sitzungsbb.* 1868, Bd. lviii. Abth. ii. p. 99.

The first few drops make the fluid dark green, and the fluid must be carefully added in order to hit the point at which the whole fluid becomes a fine green.

Nascent oxygen has a rapid action upon bilirubin. If a little binoxide of lead be carefully added to, and mixed with, a freshly prepared alkaline solution of bilirubin, the fluid acquires, before two minutes be over, the green brown colour which bilirubin has after it has simply stood exposed to the air for a few days. If a little hydrochloric acid and much spirit be added, there is at once a solution of biliverdin.

Spongy platinum lessens the time of the formation of biliverdin from a few days to a few hours. If the red brown solution of bilirubin be placed in a shallow dish, and spongy platinum thrown in, it is possible to see the change of colour pass from the platinum into the fluid around.

Permanganate of potash gives at once further oxydation products.

According to Maly the best method of preparing biliverdin is as follows: Binoxide of lead is slowly mixed with an alkaline solution of bilirubin until the fluid give a pure green precipitate with acids. The whole of the fluid is then faintly acidified with acetic acid, when there is a complete precipitation of biliverdin-lead, leaving the fluid colourless above. The precipitate is filtered off, washed till the filtrate be free from lead, then acted on by alcohol holding sulphuric acid, filtered and washed with water.

Pure biliverdin is a black shining body, but when powdered is black green. It is without taste or smell and does not readily become wet with water. When heated to 100° C. it gives up some amount of water. At this temperature it remains unchanged in weight, but after being thus dried becomes very hygroscopic.

The purest biliverdin is soluble in alcohol. The solution is not deep green, but rather sap green. As

soon, however, as a trace of acid be added (hydrochloric, sulphuric, or acetic) the whole becomes of a fine green.

If to the alcoholic solution of biliverdin a little ammonia and chloride of calcium be added, a dark green precipitate, insoluble in water, is thrown down: if nitrate of silver be added, a dark brown precipitate is thrown down in flakes, with complete decoloration of the fluid. This biliverdin-silver is not soluble in water, but is easily soluble in ammonia with dark chestnut colour. Biliverdin-lead prepared in the same way is in brown green flakes.

Rubbed up with concentrated sulphuric acid, biliverdin is dissolved with a green colour, and is thrown down unchanged by water, in green flakes which are soluble in alcohol.

In caustic alkalies and their carbonates, it is dissolved with a sap green or brown green colour. It is soluble in small amount in æther, and not in chloroform. If, however, the chloroform hold a little alcohol, it dissolves the biliverdin readily. It is also soluble in glacial acetic acid, in chloroform and glacial acetic acid mixed, and also in ordinary strong acetic acid, with remarkably fine colour.

Biliverdin is not soluble in benzol, sulphide of carbon, very slightly soluble in amylic alcohol and iodine-æthyl, but if these two bodies contain a little æthylic alcohol, they dissolve biliverdin with ease.

Methylic alcohol dissolves biliverdin as readily as ordinary alcohol.*

Bilifuscin. It seems to be agreed by all chemists that bilirubin and biliverdin are present in the bile, and are the chief colouring matters of the secretion. Städeler, however, describes a series of pigments, the existence

* Maly, *Sitzungsberichte d. math.-naturw. Classe d. kaiserlichen Akademie*, Wien, 1868, Bd. lvii. Abth. ii. p. 104.

of which is not admitted by others. One of these pigments is bilifuscin, which Städeler finds in the dark brown green residue which is left in his method after the action of hydrochloric acid upon the bilirubin from gall stones. (See page 28.) Boiling chloroform dissolves the bilirubin, and the extracts are at first dark coloured, and leave by evaporation a very dark residue, which liquifies in the heat of a water bath, and becomes crystalline on cooling. If this mass be treated with absolute alcohol, a brown pigment, with other matters, is extracted. This brown pigment Städeler calls bilifuscin. To obtain it out of the alcoholic solution, the fluid is evaporated to dryness, and the black brown residue treated with absolute æther. The æther takes up a part of the pigment and the palmitic acid and other fatty acids. The bilifuscin, insoluble in the æther, is found to be scarcely soluble in chloroform. It is an almost black, shining, brittle body, which in powder is almost olive green.

With nitric acid it gives the same play of colours as bilirubin. From the elementary analysis, Städeler gives the formula: $C^{32}H^{20}N^2O^8$, on the old notation. It is therefore, only bilirubin with two more molecules of water. After incineration it leaves no ashes.

When much diluted, the solution in alcohol shows the same colour as deeply jaundiced urine. It appears to be almost insoluble in æther, chloroform, and water. It appears to be soluble in alkaline solutions and to form a compound with lime as bilirubin does, but much less bulky.*

If bilirubin be heated with hydrochloric acid, a dark brown appearance is formed, due, Städeler thinks, to the presence of his bilifuscin.†

Biliprasin. Städeler's second pigment, biliprasin, is

* Städeler, *Arch. d. Chem. u. Pharm.* 1864. Bd. cxxxii. pp. 326 and 337.

† Städeler, *ibid.* p. 334.

got when the residue from the gall stones gives no longer any brown pigment, and acquires a bright olive colour. It still contains much bilirubin, and also a green colouring matter, biliprasin, which dissolves in alcohol with a fine green colour. It is removed by repeated treatment with spirit, and then the bilirubin completely extracted with boiling chloroform. To prepare the biliprasin from the alcoholic solution, which also contains a very small amount of bilirubin, the solution must be evaporated to dryness, and the residue powdered and treated with æther and chloroform. It must then be dissolved in a very little cold spirit, and the filtered deep green solution evaporated to dryness. The pure biliprasin remains as a shining, almost black, brittle crust, like bilifuscin; when powdered it has a greenish-black colour. It becomes fluid on being heated, shows bubbles and sends off peculiarly smelling vapours which are but little coloured. When incinerated it leaves about 0.6 *per cent.* of ashes of weak alkaline reaction but not effervescing with acids. The formula according to Städeler is $C^{32}H^{22}N^2O^{12}$ on the old notation.

Very little biliprasin is found in gall stones. It is insoluble in water, æther, and chloroform, while it is easily soluble in alcohol with green colour. The solution of biliprasin becomes brown with ammonia, and this distinguishes it from biliverdin. It gives a fine play of colours with nitric acid; it is easily soluble in the pure alkalies, but less in the carbonate of soda. If acids be added to the alkaline solution, the green colour returns, and the solution is no longer brown. This reaction is seen in jaundiced urine. Städeler thinks that the colour of this urine is due chiefly to biliprasin.*

Bilihumin is the body which remains behind when the gall stones have been treated with æther, water,

* Städeler, *Annalen d. Chemie*, 1864, Bd. cxxxii. p. 339.

dilute acids, chloroform, and spirit. In order completely to free it from the pigments spoken of above, it is washed with ammonia water, and remains as a black brown powdery body. Städeler made no elementary analysis of it for it still contains epithelium and mucus, and is therefore impure. It shows a play of colours with nitric acid.

Blue pigments have been mentioned by several chemists when treating of the constitution of the bile. Städeler, in speaking of the products of the oxydation of bilirubin, pointed out that a blue pigment could be got as one of the stages, and thought it probable that this blue pigment had some relation to the indigo colouring matter of the urine.* Maly likewise described more in detail the blue product of the oxydation of bilirubin.†

Ritter has described a blue pigment in the bile of man, oxen, sheep, pigs, dogs, and cats, and which he isolates by the following process: the bile is filtered and shaken with chloroform; the chloroform is separated by decantation, and then shaken up with a weak solution of soda; this is afterwards neutralised with hydrochloric acid; the two layers are separated, the watery holding the blue matter in suspension. This blue pigment is insoluble in chloroform or acids. Its alkaline solution is colourless or yellow. The only difference between the new body and indigo is, that the solution of the former in an alkaline glucose fluid, if neutralized by an acid and exposed to the air, does not allow a red compound to be deposited until a few days be over, or even as much as a month; while in like solutions of indigo the colour becomes immediately blue.‡

Jaffe also says that if the impure solution of bilifuscin,

* Städeler, *op. cit.* p. 333.

† Maly, *Sitzungsberichte d. math.-naturw. Classe d. k. Akad. d. Wissenschaften*, Wien, 1869, Bd. lix. Abth. ii. p. 601.

‡ Ritter, *Bulletin mensuel de la Société chimique de Paris*, 1870, t. xiii. p. 212.

which is obtained when the chloroform extract of gall stones is acted on by absolute alcohol, be acidified and exposed to the sunlight, the solution, at first of a dirty brown, passes in an hour or two into a fine blue, and this without any intermediate stage of green. It shows three absorption bands in the spectrum, but Jaffe has not had an opportunity for further study of the body.*

Bilicyanin. Heynsius and Campbell have described the changes which the spectrum of the bile pigments undergoes in oxydation. They find that all the pigments which Städeler describes give, when oxydised, a violet blue pigment which at first shows bands at C and E, later only one band at F. The place of this band, therefore, agrees with that described by Jaffe. The same body arises also by the action of other oxydising agents, and it was possible to obtain the body in substance by treating bilirubin with bromine water, washing with water, shaking up with chloroform, and evaporation of the extract. Heynsius and Campbell called this new body bilicyanin on account of its deep blue colour. It appears that Stokvis had before them described a body identical with this, but named it choleverdin;† he has, however, withdrawn this name, and now uses only bilicyanin.‡ Heynsius and Campbell find that if the oxydation of bilirubin by means of nitric acid be allowed to proceed so far that only the band at F be visible, and if then the solution be thrown into a large amount of water, brown flakes of choletelin are thrown down. This body in acid solutions shows the band at F; in alkaline solutions it does not immediately show the band described by Jaffe and marked with d, but it does show it after the addition of chloride of zinc, with-

* Jaffe, *Arch. f. d. ges. Phys.* 1868, Bd. i. p. 271.

† Stokvis, *Maandblad v. h. Genootsch. ter bevord van nat.- gen.- en heelk. te Amsterdam*, 1870. s. 10. I have not seen this article. I borrow the reference from Heynsius and Campbell.

‡ Stokvis, *Journal of the Chemical Society*, 1873, vol. xxvi. p. 288.

out the exhibition of fluorescence. This choletelin they consider identical with the urobilin of Jaffe.

Bilicyanin they always find in human gall stones, when these are boiled with hydrochloric acid after complete exhaustion with solvents. It is never found in fresh bile, but is formed quickly in the alcoholic extract by standing exposed to the air. Choletelin was found in two gall stones, very often in jaundiced urine; bilicyanin, however, was found only once and that but for a short time.*

Dr. Thudichum has given many spectra of derivatives of the colouring matters of the bile, which he describes and names. The reader is referred to his work for further information.† Likewise Städeler at the end of his essay describes certain green colouring matters which give a decided Gmelin's reaction.‡

* Heynsius and Campbell, *Centralblatt f. d. med. Wiss.*, 1872, p. 696.

† Thudichum, *Tenth Report of the Medical Officer of the Privy Council*, Lond. 1868. p. 251.

‡ Städeler, *op. cit.* p. 348.

CHAPTER III.

THE FATS, SALTS, GASES, AND OTHER CONSTITUENTS OF BILE.

CHOLESTEARIN, though found in the bile, is not peculiar to it as the bile acids are, but it is found widely distributed in various other parts and fluids of the body. Full descriptions of it may be found in the chemical hand-books, and I shall therefore not attempt to give an exhaustive account of its chemistry.*

The most common method of preparing cholestearin is from gall stones, which ordinarily contain a large amount of this body. They are powdered and then extracted with boiling alcohol, the solution being filtered while hot. On cooling, the cholestearin separates in crystals, which must be purified by being dissolved in boiling alcoholic solution of potash, allowed to separate on cooling, and again washed with cold alcohol and water. Last of all they must be again dissolved in alcohol and æther, and the solution allowed to evaporate to crystallization. In this way cholestearin may be got from the alcohol and æther out of which the bile acids have crystallised.

Cholestearin is insoluble in water, but soluble in boiling alcohol, in æther, chloroform, and benzol. It crystallises from alcohol in flat rhombic tables; from chloroform, benzol, and æther, in anhydrous shining fine needles. The flat tables often need a very fine

* A name was first given to the crystalline principle of gall stones by Chevreul (*Annales de Chimie et de Physique*, 1816, t. ii. p. 346.) He called it *cholesterine*, from *χολή* bile, and *στερεός* solid. To my mind a better name is cholestearin, from *χολή*, bile, and *στέαρ*, fat, as it is by no means the most important part of the solids of the bile, but is only the fat of the bile. The Germans formerly spelt the word in this way. Of late they have followed the French.

opening in the stage of the microscope to allow them to be seen.

The formula for cholestearin is $C^{26}H^{44}O^2$. It was shown by Berthelot to be a monatomic alcohol.* The olefiant gas of the series is cholestearilin, $C^{26}H^{42}$; obtained by the action of strong sulphuric acid on cholestearin.

Cholestearin fuses at $145^{\circ}C$. and can be sublimed in sealed tubes without change at $360^{\circ}C$. Solutions of cholestearin have a levo-rotatory action on polarised light, for yellow light, -34° ; for red, $-27^{\circ}.5$; for white, $-39^{\circ}.5$.†

Although cholestearin be insoluble in water, yet it is held in solution in the bile by the action of the alkaline salts of the bile acids, which, like soaps, are able to dissolve cholestearin.

With strong sulphuric acid and iodine a violet colour is given; with chloroform and sulphuric acid, a blood-red colour, changing to purple.

Lecithin, a body containing phosphorus, is also found in the bile. Like cholestearin it is not peculiar to the bile, but is found in greater abundance in the nervous tissues. By some it has been thought akin to Oscar Liebreich's protagon. It is also found in the yolk of egg, semen, white corpuscles, and serum, accompanied by cholestearin.

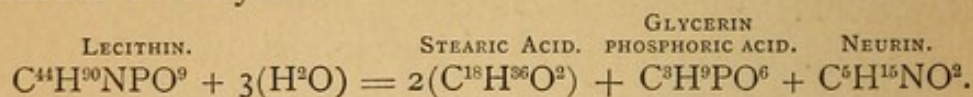
After yolks of egg have been freed from fat and cholestearin by means of æther, they are extracted with warm absolute alcohol. This alcoholic extract is concentrated and then exposed to a cold of $-10^{\circ}C$. A precipitate is thrown down of lecithin. Another method is to throw down the alcoholic solution of lecithin with chloride of platinum with which it forms crystals.

* Berthelot, *Annales de Chimie et de Physique*, 1859, t. lvi. p. 51.

† Hoppe-Seyler, *Arch. f. path. Anat.* 1858, Bd. xv. p. 129.

Lecithin is a yellowish mass, not crystalline, and very hygroscopic ; though insoluble in water, it swells up in water and becomes white and milky. It is insoluble in acids and alkalies, and chloride of sodium. Æther dissolves it easily ; cold alcohol, a little ; hot, readily.

By boiling with baryta water, lecithin is decomposed into neurin or cholin, glycerine-phosphoric acid, and stearate of baryta :



According to Diakonow, lecithin may exist in combination with each of the three fatty acids ; as distearin-lecithin, dipalmitin-lecithin and diolein-lecithin. He looks upon it as a salt of distearyl-glycerin phosphoric acid in combination with neurin as a base.*

Neurin or Cholin. In 1849† Strecker discovered in the bile of pigs a body which in 1862‡ he found also in ox bile. This body he named cholin ; and it is prepared by the following method : Fresh ox bile is decomposed by boiling with baryta water ; by this the greater part of the colouring matter, mucus, fat, and cholestearin is thrown down. To the filtered solution much hydrate of baryta is added, and the whole is boiled for about 12 hours. Sulphuric acid now throws down both the baryta and the cholalic acid, which may be separated from one another by means of boiling alcohol. The filtrate is now evaporated on a water bath, and so much sulphuric acid added as to drive out the hydrochloric acid completely. By treating the remainder with spirit, the sulphates remain behind with the taurin and a part of the sulphate of glycocoll. The alcoholic solution is evaporated so as to drive off the

* Diakonow, Hoppe-Seyler's *Med.-Chem. Untersuchungen*, Berlin, 1866-71, pp. 221 and 403.

† Strecker, *Annalen d. Chemie u. Pharm.* 1849, Bd. lxx. p 196.

‡ Idem, *ibid.* 1862, Bd. cxxiii. p. 353.

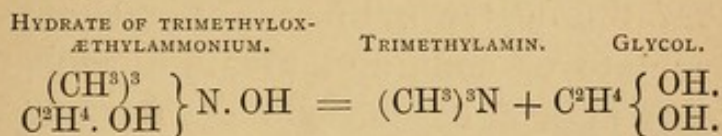
ammonia and is then boiled with hydrate of litharge. The filtrate is freed from lead by sulphuretted hydrogen and after evaporation and extraction with alcohol, the solution is decomposed with a little hydrochloric acid and chloride of platinum: there is thrown down a precipitate of a body formed by cholin in combination with chloride of platinum.

The formula for this is $C^5H^{15}NO$, $HCl + PtCl^2$. Cholin when free would be an ammonia base whose formula would be $C^5H^{13}NO$. The rational formula is unknown; but it may be an amylenoxyd-ammonia, $C^5H^{10}O$, NH^3 ; or an æthyloxyd-trimethylamin C^2H^4O C^3H^9N .

Cholin is with difficulty soluble in absolute alcohol, but readily in dilute. Strecker has obtained cholin in combination with carbonic, sulphuric, nitric, and oxalic, acids.

Both Dybkowsky* and Baeyer† believe that Strecker's cholin is identical with the body which O. Liebreich has obtained from brain substance and which he calls neurin.‡

According to Würtz, neurin is hydrate of trimethylox-æthylammonium§ which is changed by heat into trimethylamin-glycol.



It would seem probable that it is the lecithin in the bile which is the source of the neurin; for lecithin easily breaks up, and one of the products of its decomposition is neurin. Trifanovsky, however, takes another view, and believes that the neurin exists in the bile in some combination with either the biliary or the

* Dybkowsky, *Journal f. prak. Chemie*, 1867, Bd. c. p. 153.

† Baeyer, *Annal. d. Chemie und Pharm.* 1866, Bd. cxxl. p. 306.

‡ O. Liebreich, *ibid.* 1865, Bd. cxxxiv. p. 29.

§ Würtz, *Journal f. prakt. Chemie*, 1868, Bd. cv. p. 411.

fatty acids.* Both of these opinions are of course pure hypotheses.

Organic Salts. Some soaps, salts of the fatty acids, palmitate, stearate, and oleate of soda are found in the bile. The salts of these acids were noticed to be present in the bile by Tiedemann and Gmelin.†

Dogiel has noticed the presence of acetic and propionic acid in the fresh bile of oxen. The bile was decomposed by boiling with baryta, the baryta and cholalic acid thrown down by sulphuric acid, and the filtrate distilled. An acid fluid, smelling of butyric acid, came over. This product of distillation was neutralised by baryta, the baryta in excess removed by carbonic acid, and the fluid evaporated to crystallization. Acetate and propionate of baryta were formed.‡ It would seem quite possible that the presence of acetic and propionic acids in the bile may be products of decomposition, due to the process employed.

Urea. Popp finds urea a constant constituent of the bile of oxen and pigs. His method is to dilute the bile taken from the gall bladder immediately after death, and then to precipitate with lead, to remove superfluous lead with sulphuretted hydrogen, and then to evaporate the filtrate to dryness on a water bath. The residue consists chiefly of acetate of soda and urea.§ Jacobsen, however, found no urea in human bile freshly gathered from a biliary fistula; in one specimen a trace of leucin was found, but no tyrosin.||

Leucin. Berlin found, in the gall bladder of a *Sarcorampus papa*, a kind of vulture, crystals which, from their

* Trifanovsky, *Arch. f. d. ges. Phys.* 1874. Bd. ix. p. 497.

† Tiedemann and Gmelin, *Recherches &c. sur la Digestion*, Paris, 1826. Ière partie, p. 89.

‡ Dogiel, *Journal f. prak. Chemie*, 1867, Bd. ci. p. 298.

§ Popp, *Annalen d. Chemie u. Pharmacie*, 1870, Bd. clvi. p. 88.

|| Jacobsen, reported by Westphalen, *Deutsches Arch. f. klin. Med.* 1873. Bd. xi. p. 603.

shape seen under the microscope, he judged to be formed of leucin.* As, however, no chemical tests were used for the further identification of the body, much stress must not be laid on the observation. The ova of nematoids were found in the mucus of the bile.

Sugar. A saccharine body is said by some writers to have been found in the bile by Macbride.† And after the discovery of the sugar-making function of the liver by Claude Bernard, sugar itself was found in the bile. But this is a purely *post-mortem* phænomenon, for if the bile be examined immediately after death, no sugar can be found. The appearance of sugar in the bile is due to endosmosis from the liver itself.‡ This applies only to health.

Albumen is not found in the bile, at least in health. It is not uncommon to find it in the bile of the human gall bladder; but, as in the case of sugar, it is most commonly a *post-mortem* appearance. A very slight trace of some albuminous body was found in the two first specimens of fresh human bile examined by Jacobsen, but it is doubtful if they were not impurities.§ In former times, the mucus which is found in cystic bile in large amount was taken for albumen.||

Inorganic Salts. There is nothing peculiar about the alkaline salts of the bile. Their base is chiefly soda, the chloride being in large quantity, then phosphate and carbonate; there are also present phosphate of

* Berlin, *Arch. f. d. holländischen Beiträge zur Natur- und Heilkunde*, Utrecht, 1858, Bd. i. p. 103.

† See Platner, *Ueber die Natur und den Nutzen der Galle*, Heidelberg, 1845, p. 1. I have, however, looked through David Macbride's *Experimental Essays on Medical and Philosophical Subjects*, Second edit. Lond. 1767, especially the essay on fixed air, but I have not found the statement that bile contains sugar.

‡ Claude Bernard, *Leçons sur les propriétés physiologiques et les altérations pathologiques des liquides de l'organisme*, Paris, 1859, t. ii. p. 207.

§ Jacobsen, *loc. cit.*

|| Thenard, *Mémoires de Physique et de Chimie de la Société d'Arcueil*, 1807, t. i. p. 56.

A few months after Pflüger, Bogoljubow published a series of estimations of the carbonic acid contained in the bile of dogs, and, in one case, of a sheep. In the first analysis the bile was freshly secreted and taken at once from the hepatic duct.

CARBONIC ACID IN 100 C.C.

	UNCOMBINED.	COMBINED.	TOTAL.
1.	19.5	37.	56.5
2.	17.1	62.5	79.6
3.		25.4	
4.	12.3		
5.	10.5	2.4	12.9
6.	6.8		
7.	5.06		
8.			12.1
9.	3.16	.29	3.45
10.	15.6	.6	16.2

This last was from the bile of a sheep.

The amount of carbonic acid in the bile is especially noteworthy, and would seem to show that some is made in the liver, as the amount is greater than in other secretions. Bogoljubow seems to think that the freshly secreted bile holds much more carbonic acid than bile which has been a long time in the gall bladder: and that the longer the bile has been in the gall bladder the less carbonic acid it holds.*

Noel found in the bile of a dog:†

Oxygen	1.22	per cent.
Carbonic Acid	4.63	„
Nitrogen	9.13	„

Hoppe-Seyler finds that the bile taken freshly from the liver during digestion either contains no absorbed oxygen, or that it holds less than .5 *per cent.* of this gas.‡

* Bogoljubow, *Centralblatt f.d. med. Wiss.* 1869, p. 657.

† G. Noel, *Étude générale sur les variations physiologiques des gaz du sang*, Thèse de Paris, 1876. Quoted by Hoppe-Seyler.

‡ Hoppe-Seyler, *Phys. Chemie*, Berlin, 1878, p. 307.

CHAPTER IV.

PHYSICAL AND CHEMICAL APPEARANCES OF THE HUMAN BILE.

The appearances of bile seen under the microscope are unimportant and in no way comparable to those of the urine, the organic and inorganic sediments of which give to the physician such valuable information. The first person who studied the bile with the aid of the microscope appears to have been Achilles Mieg, who, in a letter to Haller, says that he found nothing particular in some ox-bile that he had looked at save round shining drops, marked at their edges, which he compares to those seen in dried gum.*

Delius not only described the appearances seen under the microscope in bile but also had them engraved. He has indeed left an almost exhaustive account of what little there is to be noted. He speaks first of certain cubical crystals from human bile which, from their pointed ends as seen in the plate, and the arrangement of their square surfaces together, might be set down as cylindrical epithelium. In ox gall he saw but few of these square crystals, but abundance of granules arranged in stellate lines. In a capon he found rounded figures, in the plate they look like oil drops, which Delius says were of a violet or blue colour. In the bile of fish he found again cubical bodies or parallelopipeds.†

Weber noted also certain round and elliptical globules, of different sizes, in general small; and smaller than those

* Achilles Mieg, *Epistol. ab eruditis viris ad Albert. Haller script.* pars iv. Bernæ, 1774, vol. iv. p. 104.

† Henrici Friderici Delii *super bile humana observationes nonnullæ microscopico chemicæ* Epistola ad Gulielmum Michaelum Richterum, Erlangæ, 1788. It is contained in Richter's *Circa bilis naturam*, Erlangæ, 1788, p. xlv.

seen in the milk and mucus.* Ducrotay de Blainville speaks of granules like fat, spots of colouring matter, and occasionally vibriones.† These vibriones were never seen by Bouisson in his observations,‡ although they were detected by Charcot and Gombault in the cystic bile of certain animals whose bile ducts had been ligatured.§ Bouisson says that the bile when seen under the microscope usually presents only a yellow layer ; sometimes a few mucus globules and tables of cholestearin. Much the same remark is made by Fauconneau-Dufresne and Mandl.||

Frerichs describes the following bodies as seen under the microscope: (i.) rounded balls, transparent or greyish, usually grouped together and removed by alcohol and acetic acid, but not by filtration. (ii.) Conical yellow bodies joined together in rows, without any nucleus that could be made out. (iii.) Certain bodies not peculiar to the bile, to wit, black or dark brown granules, which disappear on the addition of caustic potash ; apparently pigment granules. (iv.) Rarely small crystals in colourless rhombic tables of cholestearin.¶

In Gorup-Besanez' description of the bile seen under the microscope, he divides the appearances into two heads ; those constant, and those variable.

There are two constant appearances: (i.) molecular granules, very like coagulated albumen, only yellow or yellow brown, and refracting the light strongly. He thinks these are only coagulated mucus. (ii.) Epithelium of the gall bladder and ducts.

* Weber, *Anatomie des Menschen*, Bd. i. p. 163. quoted by Burdach, *Traité de Physiologie*, Jourdan's ed. Paris, 1837, t. vii. p. 440.

† Ducrotay de Blainville, *Cours de phys. gén. et comp.* Paris, 1829, t. iii. p. 140.

‡ Bouisson, *De la bile*, Montpellier, 1843, p. 23.

§ Charcot and Gombault, *Archives de Physiologie*, 1876, p. 289.

|| Fauconneau-Dufresne, *Traité de l'affection calculuse du foie*, Paris, 1851. p. 39.

¶ Frerichs, *Archiv. f. phys. u. path. Chemie*, 1845. p. 442.

The variable appearances are : (i.) Cholestearin : in 100 cases, the rhombic tables peculiar to this body were only seen three times ; in the bile of cases of chronic Bright's disease, wasting after typhoid, and hypertrophy of the heart. In the last case, the bile deposited an abundant sediment of shining particles, and 20 gall stones were already present in the gall bladder. (ii.) Crystals of margarin. (iii.) Drops of fat. (iv.) Taurin. (v.) Blood ; the bile must be concentrated to show the corpuscles : if thin, it dissolves them and it is to this that the solution of the corpuscles by the bile is to be attributed. (vi.) Pus corpuscles.*

E. Neumann has found in the bile of a man, who died of pneumonia, bodies exceedingly like the *corpora amylacea* of the prostate. They were, however, much smaller ; the largest had only a diameter of 0.028 mm. and the great number were not nearly so large. In form, they were some circular, others oval, or of no regular shape, but showing a three or four-pointed figure with angles rounded off. They all showed distinctly concentric rings. In the centre of most was a small cavity from which rents spread out towards the circumference. These bodies had a fatty look, and were coloured yellow, apparently from the bile. Iodine coloured them green, which was changed into a bluish green by dilute sulphuric acid. In the gall bladder there was a large quantity of gall stones.†

The temperature of the bile at the moment of its secretion is unknown.

Some observations on the electricity of the bile were made by Bellingeri, but they are of no value in the present state of knowledge.‡

It cannot be said that our knowledge of the properties

* Von Gorup-Besanez, *Untersuchungen über Galle*, Erlangen, 1846. p. 28, and Heller's *Archiv. f. phys. u. path. Chemie u. Microscopie*, 1846. Jahrg. iii. p. 1.

† E. Neumann, *Arch. f. mikros. Anatomie*, 1866, Bd. ii. p. 510.

‡ Bellingeri, *Memorie della reale Accademia delle Scienze di Torino*, 1827. t. xxxi. p. 314.

of human bile is in a satisfactory state. The earlier observations both on men and brutes, were all made on bile taken from the gall bladder after death, or as soon as the beasts were slaughtered. Bile, however, which has made a long sojourn in the gall bladder may be looked upon as dead bile.* It contains a far larger amount of solid matter, much mucus, and has lost the property of changing starch into sugar. It is only quite lately that an attempt has been made to study more closely the properties of active bile, freshly secreted by the liver. This has again and again been done in animals since the method of making biliary fistulæ has been found out, but in man very few opportunities have offered themselves for any prolonged investigation of this sort; biliary fistulæ, formed by disease or injury, being very rare; and in the few cases known it is only in two, and these published within the last ten years, that any accurate observations have been made.†

The two cases to which I refer are reported by H. Westphalen‡ and Johannes Ranke.§ Westphalen's case is that of a man aged 32, who had an opening made in the fifth right intercostal space for an empyema. About 400 C.C. of stinking pus came out, followed some days later by bile. From May 16. to May 30. the fæces were colourless, and during this time the observations were made.

The case of Johannes Ranke was also seen in a man, aged 38, in whom there existed a communication between the bronchi and an echinococcus sac in the

* Dr. Kemp (*Proc. of Royal Society*, 1856. Vol. viii. p. 133.) believes that the mucous membrane of the gall bladder, or the mucus secreted by it, decomposes hepatic bile.

† An early attempt at the examination of human bile is mentioned by Haller (*Elem. Phys.* Lugd. Batav. 1764, t. vi. p. 605.) "In homine cui latus apertum bilem ex vesicula emittebat, Cajetanus Tacconus cysticæ bilis solius 4. uncias vidit eodem tempore fluxisse."

‡ H. Westphalen, *Deutsches Arch. f. klin. Med.* 1873. Bd. xi. p. 588.

§ Johannes Ranke, *Die Blutvertheilung u.s.w.* Leipzig 1871. p. 144.

liver. The patient brought up a quantity of bile by the mouth, but it is a matter of necessity that the bile thus offered for examination should be impure; and the inferences, therefore, drawn from its examination are less trustworthy than those taken from a case in which the fistula opened directly upon the surface of the body.

In Westphalen's case it was found that freshly secreted bile was of bright golden yellow colour, and it was only by exposure to the air that it showed the well-known changes into brown and green. In other cases of biliary fistula, the colour has been said to be greenish yellow,* greenish,† grass green,‡ or greenish brown.§ The belief of the best physiologists, as expressed by Dr. Lauder Brunton,|| would seem to accord with the statement of Westphalen.

Westphalen and von Wittich both found the bile free from viscosity. Von Wittich examined two portions. The first was clear and limpid. The second not so clear; and after standing some hours showed a change in colour which passed into yellow brown, and at the same time a yellow precipitate was thrown down.

The highest specific gravity which Westphalen observed was 1016, the lowest 1008. The mean of 22 days' observation was 1010·4. Johannes Ranke's mean was 1025, but the sources of error in this case must not be forgotten.

The reaction was neutral or barely alkaline, according to Westphalen and Jacobsen. Von Wittich found

* MacPherson, *American Journal of Med. Sci.* 1871. Vol. lxi. p. 409. Laboulbène, *Union méd.* 1875, t. xx. p. 273.

† Grandclaude, and Dassit, in Fanconneau-Defresne's *Traité de l'affection calculeuse du foie*, Paris, 1851. pp. 307. and 311.

‡ John Harley, *Med. Chir. Trans.* 1866. Vol. xlix. p. 89.

§ Von Wittich, *Arch. f. d. ges. Phys.* 1872. Bd. vi. p. 181. An account of this case has also been published by Hertz, *Berlin. klin. Woch.* 1873. p. 161.

|| Lauder Brunton, in Sanderson's *Handbook for the Physiological Laboratory*, Lond. 1873. p. 495.

it clearly alkaline, and the same observer has shown that fresh human bile contains a ferment which has the power of changing starch into sugar. This power does not appear to be enjoyed by bile taken after death from the gall-bladder.*

In Johannes Ranke's case, the solids of the bile were found to vary from 2·69 *per cent.* to 4·01 *per cent.* In Westphalen's case the mean was 2·25 *per cent.* a much lower figure.†

In Johannes Ranke's case, the bile acids formed 40 to 78·8 *per cent.* of the total solids, the mean being 53·45 *per cent.* The fats with cholestearin from 4·8 to 22·5 *per cent.* the mean being 14·48 *per cent.* The pigments and mucus from 10·28 to 24·11 *per cent.* the mean being 17·29 *per cent.* The ash varied from 13·1 to 17·8, the mean being 14·79 *per cent.*

These figures are somewhat different from those given by Jacobsen, the chemist who analysed the bile of Westphalen's case. They are as follows:

Of the organic constituents, 3·14 *per cent.* of dry bile was soluble in anhydrous æther: of this were:

Cholestearin	2·49 <i>per cent.</i>
Fatty matters	·44 „
Lecithin	·21 „

The lecithin was estimated by the amount of phos-

* J. Jacobsen (quoted by von Wittich, *Arch. f. d. ges. Phys.* 1872. Bd. vi. p. 182. from an inaugural Diss. *de sacchari formatione fermentoque, etc.* Regimont. 1865.) finds the same power in the fresh bile of frogs, pike, carp, sheep, calves, oxen, swine, rabbits, cats, horses, geese, ducks, and fowls. Only once, however, did he find it in human bile, apparently taken from the gall bladder after death.

† In the lower animals the amount of solids seems to vary much in different tribes. Thus Bidder and Schmidt found that the fresh secretion of the liver of cats, dogs, and sheep, gave an average of 5 *per cent.* of solids; of rabbits, hardly 2 *per cent.*; but of geese and crows 7 *per cent.* The contents of the gall bladder in cats, dogs, and rabbits gave 10 to 20 *per cent.* of solids; but of sheep not more than 8 *per cent.* In geese, the amount of solids was from 10 to 20 *per cent.*; in crows it was as high as 25 *per cent.* (Bidder and Schmidt, *Die Verdauungssäfte*, Mitau and Leipzig, 1852. p. 214.) The fresh bile of guinea pigs holds, according to Heidenhain, not more than 1·35 *per cent.* and does not give a reaction with Pettenkofer's test (*Arch. f. Anat. Phys.* u.s.w. 1860. p. 648.)

phorus. The bodies insoluble in æther and alcohol, probably coloured mucin, made up 10 *per cent.* of the solids.

The alcoholic extract of dry bile contained :

Glycocholate of soda	44·8 <i>per cent.</i>
Palmitate and stearate of soda	6·4 „

that is 51·2 *per cent.* of dry bile.

Jacobsen gives the following table of the amount of the inorganic constituents:

	PER CENT. OF ASHES.	PER CENT. OF DRY BILE.	PER CENT. OF FLUID BILE.
Chloride of potassium	3·39	1·276	0·029.
Chloride of sodium	65·16	24·508	0·557.
Carbonate of soda	11·11	4·180	0·095.
Phosphate of soda	15·90	5·984	0·136.
Phosphate of lime	4·44	1·672	·038.
	100·00	37·620	0·855.

The bile contained not a trace of sugar or of any other body which would reduce copper. Urea was not present. Only in the first tested specimens were traces of albuminous bodies and of leucin found, but no tyrosin was ever discovered. Quinine and mercury were also not found in the bile when they were looked for, apparently after being administered by the mouth.

Of the better known biliary pigments bilirubin and biliverdin were detected. Copper could always be found in traces in the ash of the bile.

By decomposing the soda salts, soluble in alcohol with hydrate of baryta, glycocoll only was formed, and not a trace of taurin. The absence of taurocholic acid could also be directly ascertained, as the dried bile was completely free from sulphur.

This statement is contrary to the common belief of

physiologists. Taurocholic acid is said by Dr. Lauder Brunton to be the chief acid in human bile.*

Jacobsen later on found taurocholic acid in the bile from the gall bladders of persons dying of various diseases, in one case even as much as 14.2 *per cent.* of the dry bile. The bile also contained small quantities of iron, silica, magnesia, and a trace of copper.†

The bile taken after death from the gall bladder of healthy men killed by accident was examined years ago by Frerichs‡ and von Gorup-Besanez§ whose papers appeared almost at the same time. Analyses of the bile of persons dying of diseases not connected with the liver, have been more lately made by Trifanovsky|| and Socoloff.¶

Frerichs describes healthy bile from the gall bladder as always being of a full brown colour, in thin layers brownish yellow, never green. In old persons it is darker. Its consistence is watery and thin; only in the last drops, or in the bile of new born children is a viscid appearance seen: von Gorup-Besanez thinks that the colour of the healthy bile may pass through all shades of colour, from pale yellow to black; and that the consistence may be that of tar, or thin as water.

The specific gravity, according to Frerichs, was in three cases 1040; in one only 1032. Von Gorup-Besanez has made no observations himself on the specific gravity, but quotes John, Schübler, and Kapff as finding it 1026. Bouisson also gives the same figure.**

* Lauder Brunton, *loc. cit.*

† Jacobsen, *Berichte d. deutschen chem. Gesellschaft*, 1873. Bd. vi. p. 1026.

‡ Frerichs, *Hannoversche Annalen*, 1845. Jahrg. v. p. 42. Also in Heller's *Archiv f. phys. und path. Chemie*, 1845. p. 442.

§ Von Gorup-Besanez, Heller's *Archiv f. phys. and path. Chem.* 1846. Jahrg. iii. p. 1. and *Untersuchungen über Galle*, Erlangen 1846.

|| Trifanovsky, *Arch. f. d. ges. Phys.* 1874. Bd. ix. p. 492.

¶ Socoloff, *ibid.* 1876. Bd. xii. p. 54.

** Bouisson, *de la Bile*, Montpellier. 1843. p. 13.

The smell of the bile is said by von Gorup-Besanez to be peculiar: disgusting, and like the smell of human fæces. In my own opinion this is by no means common, and the human bile has rather an aromatic smell. The taste is notoriously bitter. The reaction was found in von Gorup-Besanez's* two first cases to be neutral, and this appears to be the case more often than that the reaction is alkaline.

The results of Frerichs' analysis of the bile of two healthy young men in a percentage are as follows:

	AGED 18.	AGED 22.
Water	86.00	85.92.
Solids	14.00	14.08.
Soda salts of the bile acids	7.022†	9.14.
Cholestearin16	.26.
Margarin and olein32	.92.
Mucus	2.66	2.98.
Chloride of sodium25	.2.
Phosphate of soda2	.25.
Phosphate of lime and magnesia18	.28.
Sulphate of lime02	.04.
Oxyde of iron	Traces	Traces.

Gorup-Besanez gives the following analyses:‡

	MAN AGED 49 BEHEADED.	WOMAN AGED 29 BEHEADED.	MAN AGED 68 DEATH BY AC- CIDENT.	BOY AGED 12 DEATH FROM WOUND.
Water	822.7	898.1	908.7	828.1.
Solids.	177.3	101.9	91.3	171.9.
Bile Acid Salts	107.9	56.5	} 73.7	148.0.
Fats }	47.3	30.9		
Cholestearin }				
Mucus with Pigment	22.1	14.5	17.6	23.9.
Inorganic Salts	10.8	6.3		

In two foetal twins of six months, Frerichs found the meconium, which he looks upon as little else but foetal bile, to have the following composition when dried:

* Von Gorup-Besanez, *Untersuchungen*, u.s.w. p. 44.

† In the original it stands 70.22. Clearly a printer's mistake.

‡ E. F. von Gorup-Besanez, *Lehrb. d. Chemie*, Braunschweig, 1862. Bd. iii. p. 469.

Cholestearin, olein, and margarin .	^{i.} 1·8	^{ii.} 15·4.
Biliary resin (bile acids) . . .	12·3	15·6.
Epithelium, mucus, pigment and salts	85·9	69·00.

Frerichs thinks the foetal bile poor in biliary salts, but rich in carbon, as the liver is almost the only organ (?) by which carbon can escape during foetal life.

Trifanovsky, under Hoppe-Seyler's direction, has made analyses of the bile taken after death from the human gall bladder. A quantity of bile, 529·611 grm. was collected from the bodies of those who died of any disease whatever; and a second quantity, 306·628 grm. from those whose livers were found free from disease. The bile was poured from the gall bladder into a vessel, filled with two thirds of alcohol, and so protected from decomposition. The results of the analysis are as follows:

Water	^{i.} 90·878.		^{ii.} 91·079.	
Solids	9·122.		8·921.	
A. Insoluble in spirit .	2·808.		1·636.	
1. Soluble in water and acetic acid . . .	0·134.	Ash.	0·323.	Ash.
.		·082.		·12.
2. Mucus and phosphate of iron	2·674.	·191.	1·311.	·013.
B. Insoluble in absolute alcohol	0·846.		1·82.	
1. Before precipitation with æther	0·76.	} 442.	1·723.	·514.
2. After precipitation with æther	0·086.)		0·097.	·06.
C. Soluble in absolute alcohol				
1. Taken up by æther .	0·835.		1·023.	
<i>a.</i> Cholestearin .	0·251.		0·335.	
<i>b.</i> Lecithin	} 0·524.		0·017.	
<i>c.</i> Fat			0·359.	
<i>d.</i> Soap	·06.		0·312.	
2. Precipitated by æther	4·633.		4·444.	

The precipitate thrown down by æther is commonly looked upon as made up of bile acids, though it certainly contains soap and alkaline salts. Trifanovsky divided it into several parts, and estimated in one the amount of sulphur, in the second the alkalies, in the third the chlorine, in the fourth the nitrogen, and lastly the amount of cholalic and fatty acids.

Cholalic acid	^{1.} 49·753.	^{2.} 38·842.
Palmitic, stearic, and oleic acids	15·095.	27·46.
Sodium as metal	3·619.	2·135.
Potassium as metal	1·106.	4·586.
Sulphur	·93.	2·5.
Chlorine	?	1·33.
Nitrogen	?	4·69.

But the total amount of these bodies, estimated separately, is considerably less than the amount given by the first analysis; so there must remain in solution in the æther some body which makes up the balance. And this is the case; it is a body rich in nitrogen, either ammonia or some organic base, not glycocholic or taurocholic acid. In reality, an organic base was procured in combination with chloride of platinum from the acid filtrate which was obtained by throwing down the cholalic acid with hydrochloric acid from its combination with baryta. From this filtrate there were obtained a few crystals of taurin and a little amorphous substance which still contained glycocoll. The combination with platinum, which was very soluble in water, showed crystals which suggested by their shape and colour some neurin compound; and this was verified by its amount of platinum; ·162 grm. of crystals gave ·052 grm. of platinum. A compound of platinum with neurin in purity would give ·0516 grm. of platinum.

It has been stated that neurin is present in human bile. According to Trifanovsky it does not arise from a decomposition of lecithin, but is more probably con-

tained as some combination with the bile acids or some fatty acids.*

Socoloff, dissatisfied with all that had been done before him, determined to make a fresh analysis. He assumed that the bile was quite natural when taken after death from the bodies of persons whose disorder brought in its train no appreciable disease of the liver; an assumption which will not pass unchallenged. He made six analyses in the following manner: the bile was evaporated at a low temperature, and the solid matters extracted with absolute alcohol till the filtrate became quite colourless. This alcoholic extract was evaporated to a small amount, and then æther added until a precipitate were no longer thrown down. After two or three days the æther was poured off and the precipitate once more dissolved in alcohol, and thrown down with æther; and this procedure repeated so long as a precipitate could be seen and the æther remained colourless. In this way, bile acid salts with chloride of sodium and potassium are found in the precipitate with æther. Further, Socoloff estimated in these salts the amount of sulphur, after Liebig's method, by fusing with potash and nitre.

The mixture of alcohol and æther, containing the soaps, fats, cholestearin, and lecithin, was distilled, the residue dried at a low temperature and completely extracted with anhydrous æther. What was insoluble in æther was looked on as soap: what was soluble in anhydrous æther was held to be fat, cholestearin, and lecithin.

* Trifanovsky, *Arch. f.d. ges. Phys.* 1874. Bd. ix. p. 492.

AGE AND SEX OF PATIENT.	MIDDLE AGED MAN CEREBRAL HÆMOR- RHAGE. LIVER HY- PERÆMIC.	BRIGHT'S DISEASE. NO DISOR- DER OF LIVER.	YOUNG MAN. PHTHISIS, LIVER HY- PERÆMIC.	MAN AGED 50. HEART DISEASE, LIVER HY- PERÆMIC.	MAN A- BOUT 50. PLEURISY AND EM- PHYSEMA, LIVER HY- PERÆMIC.	TWO BILES USED. ONE OF PHTHISIS, OTHER OF HEART DISEASE;
Solids insoluble in ab- solute alcohol. . . .	4·801	4·111	1·520	3·749	3·292	4·875.
Precipitate with æther, <i>i.e.</i> bile acids and chlo- rides of sodium and potassium	8·993	4·263	3·819	6·278	9·794	5·679.
Sulphur	·144	·071	·061	·089	·11	·081.
Taurocholic acid . . .	2·324	1·143	·928	1·449	1·782	1·317.
Taurocholate of soda. .	2·431	1·197	1·031	1·506	1·865	1·376.
Soap	1·524	2·082	1·303	1·320	1·046	1·442.

These figures represent the amount *per cent.* in fluid bile.

By this table it will be seen that human cystic bile suffers many variations in its quantitative composition. The precipitate with æther is that which is most variable; though the sulphur, and therefore the taurocholic acid, is most constant. Its mean was 23·833 *per cent.* of the precipitate with æther. The amount of soap was also nearly the same in all.* Ernst Bischoff and Lossen have made six estimations of the amount of sulphur in human bile, and they find the mean to be 1·5 *per cent.* The amount varied however from ·83 to 2·99 *per cent.* Like Socoloff, they find that glycocholic acid is the more abundant acid in human bile.† Külz, who employed a modification of Carius' method of estimating the sulphur, has in one analysis found only ·1358 *per cent.* of sulphur, an exceedingly low figure. Much the same amount was, however, found in the bile of sheep, pigs, calves, and oxen.‡

* Socoloff, *Arch. f.d. ges. Phys.* 1876. Bd. xii. p. 54.

† Ernst Bischoff, *Zeitschrift f. rat. Med.* 1864. Bd. xxi. p. 147.

‡ Külz, *Arch. f. Anat. Phys.* u.s.w. 1872. p. 98.

To sum up, then, our present knowledge of the physical and chemical characters of human bile: The appearances seen under the microscope are unimportant; freshly secreted bile is a fluid, not viscid, of a golden yellow, brown, or green colour; its reaction is usually neutral, sometimes barely alkaline; its specific gravity about 1010. It contains about 2 to 3 *per cent.* of solid matter and has the power of changing starch into sugar. This power is lost if the bile remain long in the gall bladder; it then shows a deeper colour, is brown, and is of a higher specific gravity, 1030 to 1040, and becomes viscid from the presence of mucus. The amount of solids in this cystic bile varies from 8 to 17 *per cent.* but the relation of these solid constituents to one another does not seem to vary.

The soda salts of the bile acids make up about one half of the solid constituents; they may, however, vary from 40 to 70 *per cent.* of the solids. It is known that these bile acids are formed by a combination with glycoll and taurin, but whether the cholalic acid of man be identical with the cholalic acid of the ox is not known. It is certain that a taurocholic acid exists in the bile of man, although now and then it may be entirely absent, the glycocholic acid being usually the dominating acid. This forms about three quarters of the soda salts of the bile acids, while taurocholic acid forms the remaining quarter.

It is known that bilirubin and biliverdin exist in human bile; the other bile pigments have not been found. Their amount has not been directly estimated. With mucus, it is thought to be from 10 to 15 *per cent.* of the solids.

The fatty matters, the cholestearin, the soaps, and lecithin, make up from 3 to 20 *per cent.* of the solids. They seem to vary inversely with the amount of inorganic salts. The salts may be from 15 to 35 *per cent.*

of the solid bile ; and of these salts, about two thirds are made up of chloride of sodium. The remainder consists of phosphate of soda and lime, possibly a product of the lecithin, carbonate of soda, chloride of potassium, traces of magnesia and silica, and constantly traces of iron and copper.

Urea, sugar, leucin, tyrosin, and albumen are not found in health in human bile. Lecithin and neurin are found, but it is not known if the neurin exist in combination, or be a product of the decomposition of the lecithin.

The gases of human bile have not been examined.

As this page was passing through the press, I found that a research had been published quite lately as to the composition of the cholalic acid of human bile. Hammarsten of Upsala, asserts that human bile contains bilirubin and hydrobilirubin, and that the bile acid is chiefly a glycocholic acid ; but the cholalic acid of this is quite different from the cholalic acid of oxen or swine. Bayer corroborates this statement, and gives $C^{18}H^{28}O^4$ as the formula of human cholalic acid.*

* Hammarsten and Bayer, in Maly's *Jahresbericht ueber die Fortschritte d. Thierchemie f.* 1878. Bd. viii. p. 260. Wiesbaden, 1879.

CHAPTER V.

HISTORY OF THE PHYSIOLOGY OF THE BILE: THE SOURCES OF THE BILE IN THE ŒCONOMY.

IT would seem to us, who live in the present age, that the secretion of bile would be the first function of the liver to become known. We must, however, go back to the early records of medicine to see if this were really the case. And in few matters is it more clear that several hands had a share in the collection of books which we call Hippocrates than in the teaching about the humours of which the body is composed. The writer of the book *De Morbis Lib. i.* teaches that all diseases arise from two sources, bile or phlegm,* while the writer of *De natura hominis* insists that there are four humours, the blood, the phlegm, the yellow bile, and the black bile,† the proper balance of which in the body is health, disease arising when there is excess or defect of any of these humours. On the other hand, the writer of *De Morbis Lib. iv.* teaches also that there are four humours; but in his system the black bile is replaced by the dropsy, or water.

(ὕδρωψ)‡

In the undoubted writings of Hippocrates there is but

* *De Morbis*, Lib. j. cap. ij. and *De aff.* cap. i. Littré's ed. t. vj. pp. 143. and 208.

† *De nat. hom.* cap. iv. Littré's ed. t. vj. p. 39. The four humours followed the four seasons, and it is likely that they have some relation to the four elements. See Sir Thomas Browne on the number four (*Pseudodoxia Epidemica*, Bk. iv. chap. 12. Lond. sec. ed. 1650. p. 178.)

‡ Petersen (*Hippocratis nomine quae circumferuntur scripta ad temporum rationes disposita*, Hamburg, 1839, p. 37.) however, notes that Plato in the *Timæus*, one of his undoubted works, speaks of the four humours, while in other dialogues he speaks only of bile and phlegm.

little information as to what is meant by bile.* It is a fluid, yellow and bitter,† formed from fat,‡ seen indeed in the upper part of the digestive canal,§ but also found in the head and chest.|| It would seem doubtful if the yellow bile were anything more than some fluid or secretion that was yellow and bitter without any connexion with the liver; thus a yellow appearance of the back of the tongue, with a bitter taste, would be set down as a bilious disorder. And it is not till we come to *De Morbis Lib. iv.* that we find any suggestion as to the source of the bile. Speaking of the four humours which, it has been said, are, according to this writer, blood, phlegm, water, and bile, he says the blood is from the heart, the phlegm from the head, the water from the spleen, the bile from the spot which is upon the liver.¶ Later on the same writer says: "Now I will speak of the bile, how and why it grows in the body, and how the part which is upon the liver draws it to itself. This is how it is: If a man have eaten or drunken something that is bitter, or perhaps bilious and light, and the bile becomes more abundant in the liver, forthwith the liver suffers, which the children call *cardia*; and we have seen, and it is plain to us that it comes from the food and drink: for the body draws to itself from the food all of the aforesaid humours: and the place which is on the liver draws to itself all that is bilious."**

* It is plain that bile must have been talked about long before Hippocrates; the word *χολή* has cognates in the Sanscrit, Latin, Teutonic and Slav languages. The porta of the liver was also the part inspected in the sacrifices, so that it is likely that the gall bladder and its contents would early become known. The heart was inspected as well at a much later date.

† Hippocrates, *de veteri medicina*, cap. xix. Littré's ed. t. i. p. 619.

‡ *Epidem. Lib. vj, Sect. v. § 8.* Littré's t. v. p. 319. See also Sect. vi. § 1. p. 323. Liebig revived the notion that bile was formed from fat (See *Animal Chemistry*, Lond. 1842. p. 148.)

§ *De diaeta in acutis*, cap. 9. Littré's ed. t. ij. p. 295.

|| *De diaeta in acutis*, cap. 11. Littré's ed. t. ij. p. 311.

¶ *De Morbis*, Lib. iv. cap. 33. Littré's ed. t. vii. p. 544.

** *De Morbis*, Lib. iv. cap. 36. Littré's ed. t. vii. p. 550.

Aristotle, in his *History of Animals*, has noted, with considerable accuracy, the tribes in which the gall bladder is absent. Stags, he says, have no gall [bladder], but they have a colour in their tail which resembles gall; although their intestine is so bitter that dogs will not eat it, unless the stag be very fat. So also the livers of elephants are without gall [bladders]; yet if cut into, a bilious fluid will come out.*

In another place he says that the livers of those animals that have no gall [bladders] are well coloured and sweet. And of those that have gall, that part of the liver, which is under the gall, is most sweet. But those animals which have a liver not well tempered have also blood less pure; and hence the excrement which is called gall is secreted from them. And a little further on he says: Gall therefore is alone the excrement of the liver.†

The views of Galen are also very obscure as to the place where the bile is secreted. He reprobates the opinion of Asclepiades that the yellow bile was formed, not separated, in the bile passages,‡ and speaks of the gall bladder as collecting the bile;§ and that it receives the secretion, and casts it forth again.|| But in another passage he compares the functions of the spleen and the gall bladder in purifying the blood; the former purging it of the black bile; the latter of the bilious and serous humours.¶

Areteus seems to have taught that both the liver

* Aristotle, *History of Animals*, Book ii. chapt. xv. Taylor's trans. Lond. 1809, p. 58. Doves have no gall bladders; and it is from this fact that they are the emblems of guilelessness.

† Aristotle, *On the movement of animals*. Book iv. Chapter ii. Taylor's trans. p. 114.

‡ Galen, *De nat. fac.* Lib. i. cap. xiii. Kühn's ed. vol. ii. p. 40.

§ *De anat. admin.* Lib. vi. Cap. viii. Kühn's ed. vol. ii. p. 569.

|| *De nat. fac.* Lib. iii. cap. xiii. and in *Hipp. lib. de aliment. com.* Lib. iii. cap. xxiii. Kühn's ed. vol. ij. p. 187 and vol. xv. p. 352.

¶ *De atra bile*, Cap. viii. Kühn's ed. vol. v. p. 140.

and the gall bladder were concerned in the secretion of bile: he says that if the liver be inflamed or scirrhus, but remain unchanged as to its function, then it begets (τίκτει) bile in the liver; and the bladder which is in the liver separates (διακρίνει) it,* but if the passages which convey the bile to the intestine be obstructed, then jaundice is caused. Here is more clearly expressed, of which one finds many traces elsewhere, the doctrine that in the liver the bile is formed, with the urine, black bile, and blood; but that the function of the gall bladder is to separate and collect the bile, just as the kidneys and spleen separate and collect the urine and black bile.

The teaching of Avicenna† would seem to be much the same as that of Aretaeus. He says that the blood is formed in the liver; and in it, the bile and black bile, and watery humour (*i.e.* the urine) are separated:‡ and that the gall bladder draws to itself the subtle humour proper to it with the yellow bile.

Phineas Fletcher's *Purple Island* is a treatise in rhyme on the physiology of this little kingdom, man: and the opinions set forth in it may be taken as the popular belief in the days just before Harvey. In it the liver, not the gall bladder, is indicated as the seat of the secretion of the bile.§

Yet immediately after the Harveian Revolution, strange doctrines began to be taught as to the source

* Aretaeus, *On the causes and symptoms of chronic diseases*, Book i. chapter xv. Adams' ed. p. 324.

† Avicenna, *Opera*, Lib. iii. fen. 14. tract. i. *De anatomia hepatis*, Venetiis, 1608, Lib. i. p. 750. and p. 791.

‡ I have read somewhere, I think in Daremberg's *Histoire des Sciences médicales*, that Albert and S. Thomas have strange views on the functions of the liver. It would be ill work looking into two such voluminous schoolmen without some guide; but I have found only two references to the word *jecur* in the ample index prefixed to the Venice ed. 1595 of S. Thomas; the views of Albert in the treatise *de somno et vigilia* (Tract ii. cap. iii. ed. Lugd. 1651. t. v. p. 75.) seem to be merely that the liver is the seat of the natural spirits, as the head is of the animal, and the heart of the vital.

§ Phineas Fletcher, *Purple Island*, Canto iii. Cambridge, 1633. p. 29.

of the bile. De Back, a physician of Rotterdam, set forth that the bile was not made by the liver, but by the coats of the gall bladder.* Sylvius propounded the same doctrine, but more at length: he says that the bile is formed from the blood brought by the cystic arteries to the gall bladder, and thence by the coats of the gall bladder it penetrates into the cavity. From the gall bladder it descends into the ducts; by the hepatic duct it ascends into the liver, and thence passes to the heart; by the common duct it passes into the intestine.†

This doctrine of Sylvius was supported by Vieussens who says that he has demonstrated by experiment that the gall bladder is the only part of the body destined to separate the bile from the blood;‡ and according to Haller,§ the doctrine must have survived into the middle of the eighteenth century. Morgagni, too, considered it necessary to prove that obstruction of the cystic duct did not cause jaundice.||

Perverse as this teaching seems, there is yet something beyond it. G. E. Stahl says that there had been some who did not acknowledge that the bile was secreted by the body generally, and then at last excreted by the liver; but who had persuaded themselves that the bile was formed from the more subtle parts of the food, and ascended into the gall bladder through the

* Jacobi de Back, *Diss. de corde*, Cap. vj. Lond. 1660. p. 379. The edition which I have seen is bound up and pagged with Harvey's *Exercitationes*, Lond. 1661.

† Sylvius, *Praxeos Med. Lib. i. cap. xlv. §§ ii. and iii. Op. med.* Amstelod. 1679. p. 296. The Oxford editor of Nemesius, a Bishop of Emessa in the fourth century, says in his preface that the doctrine of Sylvius as well as that of the circulation of the blood was anticipated by Nemesius. I do not think that either claim holds good.

‡ Raymond Vieussens, *Traité nouveau des liqueurs du corps humain*, Toulouse, 1715. p. 355.

§ Haller, *Elem. Phys.* Lugd. Batav. 1764. t. vj. p. 587. I have not been able to see the authors whom Haller quotes.

|| Morgagni, *de sedibus etc.* Epist. xxxvii. § 10.

common duct.* I have not found this theory anywhere but in Stahl.

Malpighi did great service for the physiology of the liver and the bile; he pointed out that the liver was a conglomerate gland, made up of hexagonal or polygonal acini, not a mere mass of blood, as was once believed; that the bile duct was the excretory duct of the liver, as the ducts of the parotid, pancreas, &c. are to those glands; that the bile was made in the liver and passed into the intestines by the duct.†

For the last hundred years it has been the undisturbed belief of physiologists that the bile is excreted by the liver, and not by the gall bladder or ducts.

Source of the bile.—It was the opinion of Liebig that, in man and herbivorous animals, the bile was formed chiefly from the elements of the food which contain no nitrogen.‡ It was thought that the formula of cholalic acid ($C^{24}H^{40}O^5$) showed its kindred to the fats. Redtenbacher found capric, caprylic, and valerianic acids amongst the products of decomposition of choloidic acid.§ Von Gorup-Besanez thought choloidic acid and cholic, *i.e.* cholalic acid, but links in the chain of the decomposition of the fats:¶ and it was a favourite theory, some five and thirty years ago, that the bile was derived chiefly from the decomposition of the fats; in fact, a return to a much older belief that the bile was a kind of soap.¶¶ Lehmann noted that the portal vein held a large quantity of fat, which had disappeared in the blood of the hepatic vein, and he thought that this

* G. E. Stahl, *Physiolog.* Sect. j. membr. vii. Arct. iv. De bilis secretione.

† Marcelli Malpighii, *De viscerum structurâ exercit. anat.* Londini, 1669. *De Hepate*, cap. vii. is a refutation of de Back and Sylvius.

‡ Liebig, *Animal Chemistry*, Lond. 1842. p. 168.

§ Redtenbacher, *Annalen d. Chemie und Pharm.* 1846. Bd. lviii. p. 166.

¶ Gorup-Besanez, *ibid.* 1846. Bd. lix. p. 158.

¶¶ It has already been noted (p. 74.) that Hippocrates thought bile was formed from the fat.

fat might serve in the secretion of bile.* Bidder and Schmidt, however, noticed that upon an exclusive diet of fat, the secretion of bile at once fell to the level of that in an animal from whom all food was withdrawn; so that they think that the nitrogenous elements of the food must be looked on as the chief source of the bile.† H. Nasse, in his earlier work, saw, however, a great increase of the secretion of bile, when with fat nitrogenous foods were also given.‡ And a theory might be built upon these observations: the fats might be thought to furnish the cholalic acid, while the albuminous bodies, by their decomposition into taurin and glycocoll, gave these bodies to unite with the cholalic acid and thus form the conjugate acids. This theory is Kütke's;§ and it is undoubtedly very plausible; but the facts on which it is founded hardly bear it out; Ritter, a pupil of Nasse, made observations on the results of a fatty diet, but did not obtain any striking results.|| No deductions can, in my opinion, be drawn from his figures: and, as far as I can make out, Nasse is the only observer who has noticed much increase of bile on mixed fatty and flesh diet.

Frerichs suggested the idea that the bile might be formed from the starchy parts of the food;¶ and Kütke also supports this notion by pointing out that if from four equivalents of starch, enough oxygen be taken, the formula of cholalic acid remains.**

* Lehmann, *Physiological Chemistry*, Day's trans. vol. ij. p. 87.

† Bidder and Schmidt, *Die Verdauungssäfte und der Stoffwechsel*, Mitau and Leipzig, 1852. p. 236.

‡ Nasse, *Commentatio de bilis quotidie a cane secreta copia et indole*, Marburg, 1851. p. 14.

§ Kütke, *Zur Function der Leber*, in Heynsius' *Stud. d. phys. Inst. zu Amsterdam*, Leipzig and Heidelberg, 1861. p. 24.

|| Ritter, *Einige Versuche ueber die Absonderungs-Grösse der Galle von d. Nahrung*, Diss. Inaug. Marb. 1862. p. 33.

¶ Frerichs, in Wagner's *Handwörterbuch d. Physiologie*, Braunschweig, 1846. Bd. iii. p. 831.

** Kütke, *op. cit.* p. 22.

4 eq. of starch $C^{24}H^{40}O^{20}$
 1 eq. of cholalic acid $C^{24}H^{40}O^5$.

Ritter, however, found that in a dog fed only on potatoes, or on potatoes and fat only, the amount of bile daily secreted fell very low.*

The amount of nitrogen in glycocoll, and of nitrogen and sulphur in taurin would certainly seem to point to an origin in the albuminous bodies of the blood or food.† Some part of these bodies is thought to be split up in the liver into taurin and glycocoll, while another part goes to form leucin, tyrosin, xanthin, and hypoxanthin, bodies containing nitrogen. Meissner would probably go a step further, and say that urea also was formed abundantly in the liver. Do the peptones at once furnish these nitrogenous bodies, or are they derived from the products of the decomposition of the tissues? Karl Voit would answer that the bile acids are derived, like urea, from the tissues,‡ while the great dependence of the bile-making functions upon the glycogenetic function would seem rather to suggest that they come immediately from the splitting up of the peptones.

Kütke has suggested an ingenious hypothesis as to the relations of the bile to the making of glycogen, which may be conveniently spoken of here. He found that when the bile is diverted from the intestine, no glycogen is formed in the liver; for example, when a biliary fistula is set up; or, as later experiments have shown, when the common duct is tied. Also in Moos' experiments of tying the portal vein, no bile and no sugar was found in the liver twenty-four hours after the operation. By tying the portal vein, the return of bile

* Joseph Franz Ritter, *op. cit.* p. 32.

† See a paper by A. Froehde in Erlenmeyer's *Zeitschrift f. Chemie und Pharmacie*, 1864, Jahrg vij. p. 464.

‡ Karl Voit, *Phys.-Chem. Untersuchungen*, Augsburg, 1857. p. 41.

from the intestines to the liver by the blood would be stopped. Is it possible, then, that the circulation of the bile is needful for the making of glycogen? Kütke thought perhaps that the glycogen might take its source from the glycocoll and taurin of the conjugate acids. To prove this, food was withheld from a dog for 5 days, so that all the glycogen might disappear from the liver; then 5 grammes of glycocoll were given in water, and the dog was killed in $2\frac{1}{2}$ hours. Sugar and glycogen were found in the liver. Also with taurin the like was seen. A dog was kept without food or drink for 8 days; and on the 9th day 4 grammes of taurin in water were given to him, and the dog was killed in $2\frac{1}{2}$ hours. The liver held a good deal of glycogen and sugar, while sugar was present in the blood of the carotid.

Kütke sets forth from this the following propositions: that the bile-making function is the chief function of the liver; and that the glycogenetic is subsidiary to the biliary function; *diabetes mellitus*, therefore, depends upon a greatly increased secretion of bile, while artificial diabetes depends upon an increased change of glycogen into sugar. At the same time that glycogen is formed, urea is formed also.*

Kütke's master, Professor Heynsius, says, on the contrary, that he does find glycogen in the livers of dogs in whom a biliary fistula has been set up. Out of three dogs, it was not present in one, but plainly present to the glacial acetic acid test in two others, while iodine gave a negative reaction in two, and a dubious reaction in the third. Heynsius, however, allows that diverting the bile from the intestine greatly decreases the amount of sugar in the liver. Heynsius

* Kütke, *passim*.

Mead (*A Mechanical Account of poisons*, Lond. 1747, 4th ed. p. 32.) says that diabetes is much akin to jaundice, and is a distemper, not of the kidneys, but of the liver, proceeding from a vitiated mixture of the bile.

also found that the length of time for which Kütke kept his dogs without food was not enough completely to free the liver from glycogen. Some small amount still remains at the end of a week's fast, and this amount was not increased by giving glycocoll or taurin to the animal shortly before death.*

If these experiments of Heynsius prove correct, it will undoubtedly cause Kütke's theory of the formation of glycogen solely from glycocoll and taurin to be abandoned. Not so, however, his views of the dependance of the bile and glycogen making functions of the liver upon each other. Bernard once thought them totally distinct† and was followed by writers who held that some cells of the liver secreted the one, and others the other. The two functions have undoubtedly a close relation to one another; for the ligation of the duct, or the diverting of the bile from the intestine, causes a great decrease of glycogen in the liver, if not an entire absence from that organ.

Secretion or only Excretion by the Liver.—In the seventeenth century, Glisson taught that the liver was a mere filter, by which the bile was strained off from the mass of the blood. The business of the liver, he says, is to take up by the porta the blood charged with bilious humours, to separate the bile, and then to return the blood made pure again into the cava.‡ This doctrine prevailed quite into our own times, and was specially favoured by physicians to whom it very conveniently furnished a theory of jaundice by suppression of secretion. After Budd, the doctrine was thought to be exploded, but it was revived by Liebermeister, who

* Heynsius, *Die Quelle des Leberzuckers*, in *Stud. d. phys. Inst. zu Amsterdam*, Leipzig, and Heidelberg, 1861, p. 57.

† Claude Bernard, *Leçons sur les propriétés etc. des liquides de l'organisme*, Paris, 1859, t. ii. p. 203.

‡ Francisci Glissonii, *Anatomia Hepatis*, Cap. xli. Amstelædami, 1659, p. 456.

pointed out, quite truly, that the physiological demonstration of the secretion of the bile by the liver was wanting.*

The theory of the formation of the bile in the body at large was indeed thought to be disproved, specially by the experiments of Moleschott. He removed the whole of the liver from frogs; and found that in some cases the animals would live as long as three weeks: yet no trace of bile acids could be found in their blood, muscles, gastric juice, lymph, or urine.† Kunde preceded Moleschott in observations with the like object, but they are less valuable; Kunde's frogs survived at the most the fourth day.‡ Johannes Müller is commonly said also to have extirpated the livers of frogs; but, as his experiments are related by Kunde, he seems only to have thrown a ligature around the vessels of the liver, and afterwards to have found the same changes with nitric acid in the blood of healthy frogs as in the blood of those operated upon. ||

It may be objected to Moleschott's and Kunde's experiments, that they used chemical tests, not now very greatly trusted; for it is known that, in complex organic fluids like blood and urine, Pettenkofer's test may not at once detect the presence of bile acids. And a still further objection may be made; for when Leyden tied the bile duct only of frogs, no jaundice was seen at the end of 8 or 14 days. No trace of bile was found in the blood; and even in the liver not the least appearance of jaundice was seen.§ If no jaundice be caused by tying the duct, can any be looked for after removing the liver? The vital processes in these animals are very

* Liebermeister, *Beiträge zur path. Anat. und Klinik d. Leberkrankheiten*, Tübingen, 1864, p. 241.

† Moleschott, *Arch. f. phys. Heilkunde*, 1852, p. 479.

‡ F. T. Kunde, *De hepatis ranarum exstirpatione*, Diss. Inaug. Berolin. 1850.

|| Johannes Müller, quoted by Kunde, *op. cit.* p. 6.

§ Leyden, *Beiträge zur Path. des Icterus*, Berlin, 1866, p. 19.

slow; and warm blooded animals do not survive the severe injuries inflicted by the removal of the liver.

Schmulewitsch, again, in Ludwig's laboratory, made some observations which seemed to show that the bile is really formed from the blood by the liver. He passed dog's blood whipped, and diluted with saline solution, through the portal vein of a recently-killed rabbit, and found that the secretion of bile went on, in a less degree than in health, for two hours and more, after death.* Pflüger, however, passed a 3 *per cent.* saline solution through the liver of a recently-drowned cat in whom the *rigor mortis* was just beginning to shew itself; he found an abundant secretion of a dilute bile to take place, and to last for more than an hour. This will show that the supposed secretion of the bile was only a transudation of serum into the fine biliary passages, and a pushing of the bile secreted before death into the large biliary ducts, giving rise to the factitious appearance of secretion.†

Röhrig has repeated both Schmulewitsch's and Pflüger's experiments, and decides in favour of the former. He finds that no bile makes its appearance when only saline solution is thrown into the liver; whereas abundance appears when the animal's own whipped blood is again and again passed through it.‡

In this state of affairs, where every experiment, which tends to shew that the liver itself secretes the bile, not merely separates it, is met with another to show that the first experiment does not answer its purpose, we shall be compelled to fall back on the general principles of physiology.

* Schmulewitsch, *Arbeiten aus der phys. Anstalt zu Leipzig*, 1868, p. 113. M. Schiff says that in 1862 he made a similar experiment to that of Schmulewitsch; and after passing blood through the liver for a quarter of an hour about 17 centigrammes of freshly-secreted bile were collected (*Schweiz. Zeitschrift f. Med.* 1862. Bd. i. p. 50. quoted in *Arch. f. ges. Phys.* 1870, Bd. iii. p. 610.)

† Pflüger, *Arch. f. d. ges. Phys.* 1871. Bd. iv. p. 54.

‡ Röhrig, *Stricker's Med. Jahrbbb.* Wien, 1873. p. 2 68.

Looking then at the constituents of the bile : it will be seen that the bile acids and the bile pigment are the only two which are peculiar to it. The cholestearin, lecithin, fats, and inorganic salts are found in abundance in other parts of the body. The bile pigments and bile acids are however only found in the liver and bile ; * they cannot be found in the blood in health, even in that of the portal vein, † as the cholestearin, lecithin, and fats are. From whence it is inferred that the pigments and bile acids are formed in the liver. ‡ To this it may be objected that the facts are not good. The failure of physiological chemistry to detect bodies in no way warrants the assertion of their absence in a fluid. Of late years, even physiological chemists have succeeded in detecting both pigments and acids in the urine in health, a sure sign that they must be present in the blood, as it would not be assumed that the kidneys were able to secrete them. To this it may be said that in healthy urine the pigments and acids are present in very minute quantity and that this minute quantity probably corresponds to the amount which escapes re-excretion by the liver when the pigments and acids are taken up by the mesenteric veins and lacteals ; that the bile pigments and acids have been detected in the blood in cases of jaundice, so that if they existed in any quantity in the

* Cloez and Vulpian (*Comptes rendus*, 1857, t. xlv. p. 340) say that they have found taurocholic acid in the supra-renal bodies of herbivorous animals. They did not, however, obtain any crystalline body, but only a sulphur-containing body, nor did they even use Pettenkofer's test, or make an elementary analysis. I should hesitate in drawing any conclusions from their work.

† C. G. Lehmann could find none of the bodies peculiar to the bile in the blood of the portal vein of the horse (*Journal de Pharmacie et de chimie*, 1852, t. xxi. p. 396) nor Hoppe-Seyler in the portal blood or chyle of 5 dogs (*Arch. f. path. Anat.* 1863, Bd. xxvj. p. 536.)

‡ It may be noted that Drosdoff (*Zeitschrift f. phys. Chemie*, 1877, Bd. j. p. 233.) has found the cholestearin and lecithin in four or five times as great quantity in the hepatic as in the portal vein. Beneke believes that cholestearin and lecithin are formed in the liver, and absorbed by the intestines into the blood ; and that the liver is the source in the œconomy of these bodies. (*Grundlinien der Pathologie des Stoffwechsels*, Berlin, 1874, p. 194.)

blood in health, equal say to the cholestearin, it would be impossible that they could escape detection. I think myself this reasoning is valid; for the case of the urine of jaundice in which for so long the bile acids lay undetected is not in point, as the bile acids could not be found at any time, while it is acknowledged that they can be found in the blood in cases of jaundice or artificial injection.

But there is yet another argument. It is said that the liver is able to draw to itself and forthwith excrete whatever bile pigments may be present in the blood. Schiff found, when bile is injected into the duodenal fistula of an animal, which has also a biliary fistula, that a great increase of the secretion of bile from the biliary fistula takes place in 12 or 15 minutes after the injection. And with animals in whom an amphibolous biliary fistula had been made, that is, a fistula in which the bile could be directed into the intestine, or to the outside of the body at pleasure, it was found that a much greater amount of bile was secreted after the bile was allowed to pass into the gut than after it had been led out of the body. Further, if the bile acids were injected into the veins, stomach, or duodenum, or under the skin, a great increase in the solids of the bile took place.* Prince Tarchanoff found that when hæmoglobin or bilirubin was injected into the veins of an animal with a permanent fistula, a great increase in the amount of pigment took place.† Huppert, however, found that when the bile acids are injected into the veins of an animal with a biliary fistula, only a fourth or a third appeared in the bile,‡ and Socoloff has repeated these experiments with the bile acids, and thinks the liver has little power of ex-

* Schiff, *Arch. f. d. gesammte Physiologie*, 1870. Bd. iii. p. 598.

† Tarchanoff, *ibid*, 1874, Bd ix. p. 329.

‡ Huppert, *Arch. d. Heilkunde*, 1864, p. 244.

creting them.* Röhrig also found that when a solution of glycocholate of soda is injected into the portal vein, the pulse becomes slow, just as if the salt had been injected into a systemic vein:† an appearance which would hardly be consistent with the view that the liver has great power of rapidly excreting the bile acids.

By these observations the conjecture of some physicians, such as Dr. George Budd,‡ Skoda,§ and Dr. George Harley,|| that the bile pigments are formed in the blood, not in the liver; and that the bile acids only are formed in the liver, may be thought to be favoured. It is of course possible that the hepatic cells may, as Dr. Michael Foster says,¶ avail themselves of certain half-made materials, such as hæmoglobin, the transference of which into pigment would be easy in the opinion of many physiological chemists. From Schiff's and Tarchanoff's experiments it is argued that the liver so rapidly excretes the bile pigments, that it at once gets rid of all contained in the blood or which are formed there; so that in health no bile-pigment can be detected in the blood. I must own that these excretions must be rapid indeed: more rapid than any other excretion that is known.

What vessel furnishes the elements of the bile? It has been much disputed whether the portal vein or the hepatic artery supply to the liver the materials out of which the bile is formed. The strife, which Dr. Michael Foster thinks is over a barren problem,** has been prolonged by the observations and experiments which are brought forward, and which tend to show,

* Socoloff, *Arch. f. d. ges. Phys.* 1875, Bd. xi. p. 166.

† Röhrig, *Arch. d. Heilkunde*, 1863, p. 412.

‡ Budd, *On Diseases of the Liver*, Lond. 1857, p. 467.

§ Skoda, *Deutsche Klinik*, 1859, p. 286.

|| George Harley, *Faundice*, Lond. 1863, p. 11.

¶ Michael Foster, *Text-book of Physiology*, London, 1877, p. 191.

** Michael Foster, *loc. cit.*

on the one side, that the blood of the portal vein is not necessary to the secretion of bile, and on the other, that it is.

These experiments go back as far as the days of Malpighi, who speaks of ligature of the hepatic artery close to the cœliac trunk as an often-repeated experiment: after the ligature a large amount of dilute bile was secreted.*

Abernethy noted in a well-nourished child, of about 10 months, brought to St. Bartholomew's Hospital for dissection, that the portal vein terminated in the *vena cava inferior*, nearly on a line with the renal veins. The gall-bladder contained a teaspoonful of bile, bitter to the taste, which became green when dilute nitrous acid was added.† Abernethy was evidently inclined to the belief that the blood of the portal vein was not necessary for the formation of bile.

Under the two heads of obstruction of the portal vein and obstruction of the hepatic artery, the different observations and experiments may be arranged.

i. *Obstruction of the portal vein.* When the portal vein of a mammal is suddenly tied, the animal dies within 24 hours at least of the operation: the greater number die immediately. In four rabbits who survived the operation about 24 hours, Moos found an absence of bile and sugar in the liver. In frogs, who live

* Malpighi, *Opera*, London, 1686. De Liene, p. 120 in the *De viscerum Structura*. Benjamin Phillips says that he tied both portal vein and hepatic artery, but noticed only a decrease of the secretion of bile. (*Lond. Med. Gaz.* 1833, vol. xii. p. 423.) Simon of Metz is said to have done the same. (*Journal de Progrès*, 1828, t. vii. p. 215.) I have not verified this last statement.

† Abernethy, *Phil. Trans.* 1793, Part i. p. 61. It is just mentioned by Lawrence (*Med. Chir. Trans.* 1814, Vol. v. p. 174) that a teacher of anatomy in London had met with a like state in the body of a much older person. Benjamin Phillips (*Lond. Med. Gaz.* 1833, Vol. xij. p. 423) gives two other cases; one by Lieutaud, (*Historia Anat.-Med.* Paris, 1767, t. j. p. 190) but this is a case of absence of the liver and spleen; and another by J. J. Huber, (*Observ. aliqu. Anat.* Casselis, 1760, p. 34) in which the portal vein is said to have passed through the diaphragm, *e ramis suis hepaticis mox productus*, but nothing is said of the bile.

much longer, he found the secretion decreased during the first few days after the operation; while if the animal lived long, say four weeks, the bile was apparently increased in amount.* Oré discovered a plan by means of which a gradual obliteration of the portal vein took place. In all his dogs he found the gall-bladder full of bile.† It would, however, have been more conclusive, as Bernard remarks, if a biliary fistula had been established at the same time that the portal vein was tied,‡ as the gall-bladder may have been filled by bile secreted before the operation. In disease it is not very uncommon to find a complete obliteration of the portal vein by clots, and in these cases the gall-bladder is often full. This of course affords as much or as little proof as Oré's experiments.

Schiff, in some of his experiments on the influence of the circulation in the liver on the secretion of bile, tied all the structures in the hepato-duodenal ligament, save the hepatic artery. Occasionally, however, he tied the vessels separately; the bile was received by means of a cannula tied in the common duct. In cats, the ligature was followed by death in 40 to 90 minutes, no bile being secreted. The creatures rapidly became torpid, and artificial warmth in no way lessened this state. No rabbit survived the operation longer than 54 minutes. According to Schiff, the cause of death seemed to be the accumulation in the blood of the materials which ought to be excreted by the bile.

In dogs and cats, Schiff tied the portal vein after Oré's method, somewhat modified. In these creatures he found

* Moos, *Untersuchungen u. Beobachtungen ueber den Einfluss d. Pfortaderentzündung auf die Bildung der Galle und des Zuckers in der Leber*, Leipzig and Heidelberg, 1859. pp. 17 and 24.

† Oré, *Comptes rendus*, 1856, t. xliii. p. 463.

‡ Claude Bernard, *Leçons sur les propriétés, &c. des liquides de l'organisme*, Paris, 1859, t. ij. p. 195.

that the portal vein above the place of ligature made anastomoses for itself with the general systemic veins : in cats especially it was seen that a large branch from the umbilicus passed by the side of the *ligamentum teres* of the liver into the portal vein. To this vein Schiff gives the name of *vena parumbilicalis*. These observations do not, in Schiff's opinion, contradict the general belief that the bile is made by the portal blood. He made also an attempt to turn the blood from the renal artery into the portal vein, but the experiments did not succeed on account of the clotting of the blood in the vessels. The experiments on three animals lasted but a quarter of an hour, during which time the liver showed a dark red colour, but the secretion of bile went on.*

In another set of experiments, Schiff intended to throw light on the absorption of bile by the portal system ; he found that the amount of bile passed out of a biliary fistula in a dog whose portal vein was tied, after the injection of bile into the intestines, was no less than in one whose portal vein was free, so that the bile was absorbed from the intestines, carried into the general circulation and yet was at once discharged by the liver. It is a pity, however, that Schiff did not ascertain that no immediate communication in this dog between the intestinal vessels and the upper part of the portal vein had been set up.†

Röhrig found that if the vessels in the hepato-duodenal ligament were firmly compressed, the biliary secretion was at once arrested. If the compression did not last more than a few minutes, the liver slowly recovered itself. If it lasted longer, the animals died without another drop of bile being secreted. If the portal vein alone were compressed, there was a considerable decrease of

* Schiff, Canstatt's *Jahresbericht f.* 1862, Bd. i. p. 127.

† Schiff, *Arch. f. d. ges. Phys.* 1870, Bd. iii. p. 608.

the secretion of bile, but no such complete cessation, as there was after pressure on both vessels.*

ii. *Ligature of the hepatic artery.* It has been already said that Malpighi noted a flow of dilute bile after ligature of the hepatic artery. Brachet and Fouilhoux say that they attempted to tie the portal vein or the hepatic artery in living animals. The ligature of the artery appeared to them to suspend the secretion of bile, but not the ligature of the portal vein. They are cautious enough, however, to add that they draw no conclusions from these appearances, as the animals did not live long enough.†

Kottmeier‡ and Küthe§ found that no bile was secreted after ligature of the hepatic artery of rabbits, while Röhrig found but a slight decrease in the amount of bile secreted after the ligature of the hepatic artery;|| in what animal does not appear.

Schiff found that the ligature of the hepatic artery, behind the stomach of a large dog, was no hindrance to the secretion of bile. In fact the vessel never became empty of blood. He found in many dogs, that the ligature of the hepatic artery neither caused a stoppage of the arterial supply of blood to the liver nor of the secretion of bile. In both dogs and cats there are branches to the liver from the phrenic arteries, from the left coronary arteries of the stomach and from a small branch accompanying the bile ducts: so that it is necessary, to cut

* Röhrig, Stricker's *Med. Jahrb.* 1873, p. 242.

† Brachet and Fouilhoux, quoted by Raikem, *Observations, etc. sur quelques affections morbides de la veine porte*, in the *Mémoires de l'Académie royale de Médecine de Belgique*, 1849, p. 15.

‡ Kottmeier, *Zur Kenntniss der Leber*, Diss. Inaug. Würzburg, 1857, p. 11. Some experiments were made on frogs. In rabbits the gall bladder was found empty, and no bile in the intestines. See Cohnheim and Litten's observations on the next page.

§ Küthe, *Studien des phys. Instituts zu Amsterdam*, herausgegeben von Heynsius, Leipzig and Heidelberg, 1861, p. 35. No glycogen or sugar was found in the liver of rabbits.

|| Röhrig, *loc. cit.*

off all supply of arterial blood from the liver, that the three branches of the cœliac trunk and the phrenic arteries should be tied.* In case of ligature of the portal vein Schiff noticed no enlargement of the hepatic artery. Cohnheim and Litten confirm the statement that the arterial blood cannot be cut off from the liver by ligature of the hepatic artery in dogs. They find, however, that in rabbits this operation is possible, but is rapidly followed by death within the first 20 hours. A change in the liver takes place which Cohnheim and Litten call necrosis. On section the liver is seen to be soft, the colour grey yellow, not a trace of polish on the surface, the acini invisible: under the microscope the section is seen clouded and indistinct, and in some cases the nuclei not discernible with the help of log-wood.† These observations show the important influence which the hepatic artery has upon the nutrition of the liver; but they are not much aid in determining the question if arterial or portal venous blood be essential to the secretion of bile.

Obstruction of the hepatic artery in disease is a rare phænomenon, much rarer than portal obstruction. Ledieu has recorded a case of aneurysm of the hepatic artery in which that vessel was obstructed, and yet the gall-bladder was full of bile.‡ As the observations of Schiff teach, it is very hard to keep arterial blood out of the liver; in Ledieu's case the pyloric artery was pervious; and as this artery inosculates freely with the coronary artery of the stomach, there is no proof that the liver was deprived of arterial blood.

Reviewing these various observations, it will be at once seen that any deduction from supposed obstructions of the hepatic artery in man is of no value, and the

* Schiff, *Canstatt's Jahresbericht f.* 1862, Bd. i. p. 126.

† Cohnheim and Litten, *Arch. f. path. Anat.* 1876, Bd. lxvii. p. 162.

‡ Ledieu, *Journal de Bordeaux*, 1856, Mars. reported in Schmidt's *Jahrb.* 1857, Bd. xciii. p. 56.

whole of these may be passed by in silence. Whether the same objection will apply to obstruction of the portal vein, that is to say, whether the portal or other blood again finds its way to the liver in all cases, is not so certain. That the portal blood in many cases does not enter the liver, but the general circulation, would seem to be shown by Bernard's observation; the blood of the portal vein was found anastomosing with the renal vein, and the *vena cava inferior*, thus reproducing in mammals the venous system of Jacobson.* Other anastomoses have been described with the intestinal and external systems.

The earlier observations of the passage of the portal vein direct into the *vena cava* cannot be made of any service, as the sources of blood to the liver, other than the portal vein, are not spoken of.

The cases of sudden ligature of the portal vein which Moos records, would doubtless be set aside by many physiologists: yet it is noteworthy that 24 hours after the ligature no bile or sugar could be found in the liver; an effect hardly to be sought in the operation itself. It may therefore be thought that the sudden removal of the portal blood, the hepatic artery being free, has some influence both on the bile and sugar-forming functions of the liver, and that the functions of the liver only continue to be properly performed when the blood brought by both sets of vessels reaches the lobules. The matter is, however, a very difficult problem; and I would prefer, with Bichat,† to leave it to the decision of further researches.

* Bernard, *op. cit.* pp. 190 and 195. He indeed tied the portal vein suddenly on a pigeon: yet the animal died the next day, in spite of the communications between the portal and inferior cava in these creatures.

† Bichat, *Anatomie générale*, Paris, 1801, t. ij. p. 458. It seems to have been the general belief in Bichat's time that the bile was secreted from the portal vein. He gives fully the reasons then prevalent for this belief. Some of them seem to us foolish enough, and he has an easy task to refute them. Cf. Haller, *Elem. Phys.* Lugd. Batav. 1764, t. vj. p. 597, and Tiedemann and Gmelin, *Recherches, etc. sur la Digestion*, Paris, 1827, Partie ii. p. 57.

CHAPTER VI.

THE AMOUNT OF BILE SECRETED IN HEALTH AND THE AGENTS WHICH AFFECT IT.

Amount of bile daily secreted in health.—Before the observation of biliary fistulæ in men or animals, it was impossible to do more than guess at the amount of bile secreted by the liver. Nevertheless Haller set down the amount of bile daily secreted as 24 ounces;* a figure which approaches some of the calculations made of late years. Other physiologists about the same time set the amount much lower; a few drachms, or an ounce or two.†

Later on, more extravagant views prevailed; the amount of bile secreted in the 24 hours was calculated from the quantity thought necessary to neutralise the acid chyme, and an ox was said to secrete the enormous quantity of thirty seven and a half pounds of bile in a day.‡ Liebig adopted this statement as it coincided with some of his views on the sources of the bile and its importance in the processes of respiration and of animal heat:§ indeed the estimation seems for a time to have been generally accepted.

The views of these writers are indeed entirely speculative; and are in no way founded on observation. According to Bidder and Schmidt,|| Douglas, an Ameri-

* Haller, *Elem. Phys. Lugd. Bat.* 1764, t. vi. p. 606.

† Bianchi, *Historia Hepatica*, Genevæ, 1725, t. i. p. 116.

‡ C. H. Schultz, *de alimentorum concoctione*, Berolini, 1834, p. 108, 42 *et seqq.* quoted by Bidder and Schmidt, *Die Verdauungssäfte*, Mitau and Leipzig, 1852, p. 117.

§ Liebig, *Animal Chemistry*, Lond. 1842, Gregory's translation, p. 64.

|| Bidder and Schmidt, *loc. cit.* They quote from Tiedemann, *Physiologie der Verdauung*, Ulm, 1835, p. 268. The reference to Douglas' work is: *Medical Repository* by Mitchill, New York, 1817. I have not been able to see a volume of the *New York Medical Repository* for 1817.

can physician, was the first in this century to form any opinion based on the analogy of experiments on animals; and from these data he calculated that a healthy man excreted during the 24 hours 29 ounces of bile.

Magendie says that in dogs the escape of bile and pancreatic juice takes place by intervals; about twice in a minute a drop of bile is seen to rise from the papilla, and this drop spreads itself uniformly over the parts around.* With these two observers physiology seems to have contented herself during the first half of this century.

When Schwann, therefore, invented his mode of making biliary fistulæ in animals,† there appeared good hope that the great darkness which shrouded all that pertained to the secretion of the bile might be chased away. An increase in knowledge has certainly taken place, but the new method of observation has hardly done all that might have been looked for from it at the first moment of its discovery. One important defect is that the bile is diverted from the intestine, out of the body entirely: a circumstance not without considerable influence upon the physiology of the secretion.‡

Before considering the information given by experiments, it will be well to consider the results of the observations made in man when disease or accident has formed a biliary fistula. There are very few in which any observations have been made, and still fewer in which accurate and careful investigations have been carried out: and the observations are open to all the objections made against biliary fistulæ in animals. Further, it may be said that the observations are altogether untrustworthy, and that they were made

* Magendie, *Précis élém. de phys.* Paris, 1836, 4e. éd. t. ii. p. 14.

† Th. Schwann, *Arch. f. Anat. Phys. u. s. w.* 1844, p. 127.

‡ I must refer to special physiological works for the method of setting up a biliary fistula in animals.

on persons, all of whom were weakened by long illnesses, and most of them by a suppuration; and that the results in no way represent the qualities of the secretion in health. Of course these objections must be weighed; but the results on man, even if exhausted by disease, should be compared with those attained by observation on healthy animals, as these are the only two paths of attaining knowledge open to us.

Westphalen's observations, already spoken of in the fourth chapter of this work, are those which have been made with the greatest care.* He collected the bile passed during every four hours of the day and night. The flow showed very little variation, saving that collected from 2 to 6 in the morning, which was always small. The other amounts, collected during the day, varied from 94.3 and 83.2 gm. in the four hours, while the bile collected in night and early morning was on an average only 61.8 gm. though it was the richest in solid constituents. Of these it held 2.499 *per cent.* while the bile secreted during the day was but a little over 2 *per cent.*

The highest quantity, secreted in four hours, seen by Westphalen was 125.2 gm.: the lowest 52.2 gm. The average about 83.9. Von Wittich in his case found the quantity secreted in four hours to be 88 C.C.† The results of the two observers thus nearly agree.

The quantity secreted every twenty-four hours in Westphalen's case was on an average of 10 days 498.85 gm. The highest quantity noted was 566.7 gm. The lowest 453.1 gm. Von Wittich estimates the amount in his case to be 532.8 C.C. Johannes Ranke gives 636 C.C. as the average of five observations in his case.‡ These figures, however, are arrived

* H. Westphalen, *Deutsches Arch. f. klin. Med.* 1873. Bd. xi. p. 588. See also above, p. 61.

† Von Wittich, *Arch. f. d. ges. Phys.* 1872, Bd. vi. p. 182.

‡ Johannes Ranke, *Die Blutvertheilung*, Leipzig, 1871, p. 144.

at by allowing for the pulmonary mucus brought up with the bile. The sputa the day after the closing of the fistula amounted to 135 C.C. It is clear that Ranke's figures cannot claim strict accuracy, but only an approximation to truth. The highest number given by Ranke is 922 C.C. the lowest 405 C.C.

There are some other cases also in which the amount of bile has been estimated, but perhaps not in so careful a manner, or with so much technical knowledge. In Dr. John Harley's case, a man of 29, the amount of bile lost from the fistula during a week was from 16 to 20 fluid ounces daily (440 to 560 C.C.) associated "with absence of bile from the alimentary canal"* which I suppose may mean that the fæces were free from colour. This amount of bile daily excreted would closely agree with that given by Westphalen, Johannes Ranke, and von Wittich.† Rouis, in a case of communication with the bronchi of an abscess in the liver, found that 900 grammes of a bilious fluid were brought up in 40 hours.‡ This statement, however, is but little worth; nothing definite is said of the state of the stools or of the amount of pus or mucus present.

In the two following cases, the amount of bile daily secreted was about half of what has been given above. Dr. Robinson found, in a woman of 64, whose stools were "destitute of bile," that the amount daily discharged through the fistula was about 8 fluid ounces§ (about 230 C.C.) And in Krumptmann's case, the fæces were

* John Harley, *Med. Chir. Trans.* 1866, vol. xlix. p. 89.

† Von Wittich, *Arch. f. d. ges. Phys.* 1872, Bd. vi. p. 181.

‡ Rouis, *Recherches sur les suppurations endémiques du foie*, Paris, 1860, pp. 139 and 424. Frerichs, with his habitual inaccuracy of quotation, says that the 900 grammes were collected within 24 hours. (*Klinik d. Leberkrankheiten*, Braunschweig, 1861, Bd. ii. p. 130.)

§ Robinson, *Med. Chir. Trans.* 1852, vol. xxxv. p. 472. The fluid was pronounced to be bile by Dr. Bence Jones.

grey white, yet the daily loss of bile is said to have been only between 7 or 8 ounces.*

In Westphalen's case, the amount of solids was on an average 2.25 *per cent.* varying from 3.856 to 1.844.

The patient weighed 68 kilogrammes; so that one kilogramme secreted in 24 hours 7.34 grm. of bile with .166 solid matter.

In Johannes Ranke's case the amount of dry bile was found to vary from 2.69 *per cent.* to 4.01 *per cent.* figures much higher than Westphalen's, whose mean is 2.25 *per cent.*

The patient weighed 94lb. or 47 kilogrammes; so that one kilogramme secreted in 24 hours as *minimum* 8.61 C.C. of bile, containing .25 grm. of solid matter; as *maximum* 19.62 C.C. of bile with .8 grm. of solids.

The mean would be that one kilogramme secreted 14 grammes of fluid bile containing 0.44 gramme of solids in the twenty-four hours.

In Dr. Robinson's case the bile was noted to flow more copiously in the erect posture; probably this was due not to increased secretion but to a more rapid ejection. Dr. Robinson also says that the flow was more rapid after meals. In Westphalen's case, the chief meal was given in the middle of the day. On certain days the meal was put off for several hours, but no change in the amount or concentration of the bile was noted. On two days abundance of drink was given by the mouth; but no increased flow or marked dilution of the bile followed, while the urine was doubled in amount. A dose of calomel also was followed by no increase in the amount of bile. Quinine, given in doses of two grammes, (30 grains) could not be found in the bile.

This is all that I have been able to gather from direct observations on man. Observations upon ani-

* Krumptmann, *Lond. Med. Record*, 1873, p. 264, quoted from *Wiener Centralblatt* for March, 1873.

mals, many of which have been made with very great care and accuracy, promise to give far wider information. It must first be said that Bouisson arrived, by methods which must be thought quite inadequate to this purpose, at the conclusion that the quantity of bile daily secreted was about 6 ounces or 192 grammes. He injected water from the liver into the intestine by the hepatic duct and found that the fluid divided itself into two equal parts; one passed into the intestine; the other into the gall bladder; the amount in the gall bladder was an ounce and a half or 48 grammes. The gall bladder empties itself, he says, twice a day; and thus the amount of bile daily secreted would be 6 ounces or 192 grammes, as stated above.*

Blondlot found that the dog on whom he had established a biliary fistula secreted daily about 40 to 50 grammes. He calculates from this that man would secrete from 200 to 250 grammes of bile daily.†

Hermann Nasse, the Professor of Physiology in the University of Marburg, made in 1847 with the assistance of Platner, the first attempt at any accurate estimation of the amount of bile daily secreted by the dog.‡ He found large fluctuations in the same dog on the same diet, observations which have been repeated by the latest authorities on the same matter, the Edinburgh Committee. Nasse's work is but little known in England, probably because it was published under the form of an academical dissertation, *ad novi Prorectoris inaugurationem*.

Bidder and Schmidt made an immense number of experiments both on beasts and birds. Beginning with cats, they passed on to dogs, comparing their observa-

* Bouisson, *de la bile*, Montpellier, 1843, p. 54.

† Blondlot, *Essai sur les fonctions du foie*, Paris and Nancy, 1846, pp. 59 and 61.

‡ Herm. Nasse, *Commentatio de bilis quotidie a cane secreta copia et indole*, Marburg, 1851.

tions on these carnivorous animals with experiments on sheep and rabbits, supplemented by some on the herbivorous goose and the carnivorous crow. They give the following table as the mean of their observations.*

I KILOGRAMME OF	CAT.	DOG.	SHEEP.	RABBIT.	GOOSE.	CROW.	
In one hour secretes in grammes	0·608	0·824	1·059	5·702	·491	3·004	Liquid bile.
	0·034	0·042	0·056	0·103	0·034	0·219	Dry bile.
In twenty-four hours secretes in grammes	14·5	19·990	25·416	136·84	11·784	72·096	Liquid bile.
	0·816	0·988	1·344	2·47	0·816	5·256	Dry bile.

This table represents the mean of observations made on the following plan: a biliary fistula was established, and as soon as the gall-bladder was emptied of all its bile, and the fresh secretion of the liver began to run, the whole of the bile passed during every quarter of an hour was received in weighed glass bulbs. At the end of three hours the animal was killed; the weights of the body, liver, fluid bile, and dry bile, were then compared. The biliary fistula was made an infinite variety of times; so long after a meal, or after so much food had been given, and an average struck of all these observations for the 24 hours, for each kilogramme of weight. An estimation made on such a method hardly recommends itself. As Claude Bernard has pointed out, the stature and size of the animal are left out of consideration.† And the weight of the entire body is not at all unimportant, for Heidenhain, by comparing Bidder and Schmidt's figures for sheep and rabbits, shows that

* Bidder and Schmidt, *Die Verdauungssäfte*, Mitau and Leipzig, 1852, p. 209.

† Claude Bernard, *Leçons sur les propriétés &c. des liquides de l'organisme*, Paris, 1859, t. ii. p. 205.

as the weight of the whole body increases so the amount of bile for every kilogramme of body-weight decreases.

	GUINEA PIG.	RABBIT.	SHEEP.
Mean weight.	518.400	1525.800	23377.000
Mean amount of bile for every } kilogramme in one hour.	7.326	5.070	1.109

Now the smaller the animal the larger the liver, and *vice versa*. In guinea pigs, the ratio of weight of liver to whole body is 1: 27.3; in rabbits, 1: 33.5; in sheep, 1: 53.57. But this is not the sole cause; for 1 kilogramme of sheep's liver secretes 62.83 grm. in the hour; of rabbit's liver, 169.37 grm.; of guinea pigs, 185.54 grm.: that is, the liver of guinea pigs secretes more, weight for weight, than those of either rabbits or sheep. And this is more striking if the following figures be compared: there is secreted every 24 hours by

	GUINEA PIG.	RABBIT.	SHEEP.	
Body . . .	$\frac{1}{5.6}$	$\frac{1}{8.2}$	$\frac{1}{37.5}$	} times of own weight of fresh bile.
Liver . . .	4.467	4.064	1.507	

If, however, the amount of solids in the bile of the three animals be compared, altogether a different proportion is given. Of solid bile, each kilogramme of guinea pig secretes in the hour .098 grm. each kilogramme of liver 2.67 grm. Of rabbits, .103 grm.; liver, 3.74 grm. Of sheep, .0672 grm; liver, 3.55 grm. So it is clear that the great amount of bile secreted by the guinea pig is due solely to a large amount of water. If the amount of fluid bile for each kilogramme of guinea pig and rabbit be compared, it is 7.326: 5.070; while the proportion of solid bile is 0.002: 0.103. A more than complete reversal of the proportion.

If, too, instead of a kilogramme of body-weight, the kilogramme of liver-weight be taken, the same is observed. One kilogramme of rabbit liver will secrete

of fluid bile 169·37 in an hour, against 185·54 by guinea pig liver. Of solids, the rabbit liver secretes 3·74, against 2·67 by the guinea pig liver. Heidenhain thinks himself entitled to express the opinion, but not as a distinct doctrine, that when the amount of water passing from the liver is increased, the solids in the bile are decreased.*

A. Wolf agrees with Heidenhain as to the relation between the size of the liver and the amount of bile. He thinks that animals which are small and young, that is, whose liver is large, secrete more bile; and that the amount of the secretion is in direct ratio to the size of the liver. He has only, however, experimented on two young dogs.†

The views of the Edinburgh Committee are opposed to those of Heidenhain and Wolf. They found large variations in dogs which they could not explain either from the food or weight. They did not, however, make observations on the size of the liver, but they remark that it is improbable that this circumstance determines the amount of the biliary secretion, the great variation in the same animal from day to day being opposed to this.‡ They give a table of the average amount of bile secreted by each kilogramme of dog. (see p. 104.)

Westphalen, from his direct experiment on man, found that one kilogramme produced 7·34 grammes of fluid bile, and 0·166 gramme of dry bile in the 24 hours.§ Johannes Ranke found the mean much higher: one kilogramme produced 14 grammes of fluid bile, and 0·44 grammes of dry bile in the twenty-four

* Friedländer and Barisch, *Arch. f. Anat. Phys.* 1860, p. 655.

† Wolf, *Uwagi nad fizyologia zółci*, Warschaw, 1868. Abstract in *Centralblatt f. d. med. Wiss.* 1869, p. 86.

‡ Bennett, Rutherford, and Gamgee, *Report of the Twenty-eighth Meeting of the British Association for the Advancement of Science*, London, 1869, p. 230.

§ Westphalen, *Deutsches Arch. f. klin. Med.* 1873, Bd. xi. p. 600.

hours.* This observer tries to bring this statement into agreement with the calculations which have been made from animals. Bidder and Schmidt found that one kilogramme in a cat secreted 14·5 grammes of fluid bile in the 24 hours, and one kilogramme in a dog 20—28 grammes. For the same animal Nasse found 12·2—28·4 grammes, figures which closely correspond with those of Bidder and Schmidt. Arnold's figures are smaller: 8·1 to 11·6 grammes;† while Kölliker and Müller's are larger: their *minimum* is 21·5 grammes of fluid bile, with 0·75 gramme of dry bile; their *maximum* 36·16, with 1·162 gramme of dry bile. All these are from observations on dogs. Johannes Ranke further observes that Bischoff and Voit in their observations on the same animal came to very nearly the same figure as Ranke did with man: one kilogramme of a dog excretes 0·43 gramme of dry bile, while one kilogramme of man excretes 0·44 grm of dry bile in the 24 hours, so that Ranke concludes that man excretes as a mean about 840 grammes of bile daily, with 20 grammes of solids. I must own that I do not feel any great confidence in Ranke's figures, as he shows a disposition to use the figures of observers when they corroborate his own; but to neglect them when they are against him. This is specially to be noted in his dealings with the amount of fluid and solid bile, when he passes from one to the other according as the figures fall into agreement with his own or not.

Dr. George Scott found, as an average of three days' observations on one dog, that each kilogramme of weight secreted 23·1 grm. of fluid bile, and 1·13 grm. of solid bile, in the twenty-four hours.‡ Ritter gives,

* Johannes Ranke, *Die Blutvertheilung*, Leipzig, 1871, p. 151.

† All these figures are very conveniently given in a table put together by Kölliker and Müller (*Verhandlungen der phys. med. Gesellschaft in Würzburg*, 1856. Bd. vi. p. 461.) This table is given at p. 111, with some observations which have been published since 1856.

‡ George Scott, Beale's *Archives of Medicine*, 1857, vol. i. p. 218.

as a mean of a week's observation on one dog, 17.5 and 18.75 grammes of bile to each kilogramme of weight in the twenty-four hours.* The Edinburgh Committee gives the following table of the mean amount of bile secreted by each kilogramme of the dogs which they observed:†

NUMBER OF DOG.	FLUID BILE. grammes	SOLID BILE. grammes
1	6.47.	.412.
1	7.82.	.28.
2	5.27.	.34.
3	5.76.	.293.
4	3.53.	.146.
5	21.8.	.801.
6	20.66.	.818.
7	4.64.	.23.
8	9.24.	.305.
9	10.2.	.58.

The variations, even in observations made by the same observers, are here very great; and show how unsafe a course it is to draw conclusions from a small number of experiments.

The data for forming an opinion on the amount of bile secreted either in man or the beasts must be owned to be insufficient. The belief now prevalent among physiologists that the greater part of the bile is absorbed again by the intestines, and excreted again by the liver, must be taken into account. If this view be correct, it must be hard to arrive at any idea of the amount of bile in health by studying the amount passed out from a biliary fistula. The bile in this case is conveyed away out of the body, does not enter the intestine, and so cannot be absorbed, and again be excreted by the liver. To judge aright of the amount of bile, the quantity

* Ritter, *Einige Versuche ueber die Abhängigkeit der Absonderungs-Grösse der Galle von der Nahrung*, Diss. Inaug. Marburg, 1862, p. 11.

† Edinburgh Committee, *loc. cit.*

should be measured as it is secreted by the liver, and then passed again to the duodenum.

If we take Westphalen's mean, 500 C.C. as the normal flow from a biliary fistula, and the solids as a little over 2 *per cent.* the daily amount of solid bile will be about 10 grammes, or somewhat more.* Of these solid matters, the bile acids will form about one half; cholestearin and fats about one gramme; another gramme of pigments and mucus; while the remainder will be made up of inorganic salts; of which chloride of sodium is the greatly preponderating body, about 2·4 grammes being passed in the 24 hours. Johannes Ranke found the amount of solid bile in his patient nearly double these figures:† that is to say, of solid bile 20·6 gm. a day, of which the bile acids formed 11 grammes, the fat and cholestearin, the mucus and pigment, and inorganic ashes, all three, 3·2 gm. each. The sources of error which may have crept into Johannes Ranke's estimations, and which may have made it too high, have already been pointed out; but it is worthy of note that the figures correspond very nearly to the amount at which Ernst Bischoff calculated it in man from observations on animals.‡

Influence of food on the bile. It is commonly said, from experiments on animals, that the taking of food into the stomach is followed by an increase in the amount of bile. In Westphalen's patient, however, the chief meal was changed several hours, yet no apparent alteration in the amount or concentration of the bile followed.§ It is true that it was undesirable to allow this patient to fast, so that the immediate effect of food after a long abstinence could not be ascertained. In Dr.

* Westphalen, *Deutsches Arch. f. klin. Med.* 1873. Bd. xi. p. 600.

† Johannes Ranke, *Die Blutvertheilung*, Leipzig, 1871, p. 150.

‡ Ernst Bischoff, *Zeitschrift f. rat. Med.* 1864, Bd. xxi. p. 141.

§ Westphalen, *Deutsches Archiv f. klin. Med.* 1873, Bd. xi. p. 601.

Robinson's case it is distinctly stated that the flow was more rapid soon after meals.*

Blondlot, noted that the flow of bile in his dog, was much more abundant after food. When the animal was fasting, it sometimes, but not always, happened that several hours would go by without a drop of bile being passed; but if food were given, the bile would flow out in abundance at the end of 10 minutes or a quarter of an hour, and continue to flow throughout the time that digestion was going on.†

Claude Bernard taught that the secretion of bile took place after digestion was over. If you examine an animal with a biliary fistula, says he, you see that while the animal is fasting, nothing flows. If you give the creature food, the flow of bile does not begin at once, but at the end of a certain time, and it persists after digestion is finished. In fact, the bile of one digestion is only used in the next. The bile is collected in the bladder, which is emptied during digestion, but is filled before.‡

Bidder and Schmidt give the following as the result of their experiments on cats: the amount of bile is increased in the first hour after a meal, and before the food can have been absorbed into the blood. This is apparently simply a consequence of the increased flow of blood to the digestive organs. The increase of secretion reaches its highest point 12 to 15 hours after the meal have been taken, when it is probable that all the food has been completely digested and absorbed into the blood mass.§ From this, the amount of secretion

* Robinson, *Med. Chir. Trans.* 1852, Vol. xxxv. p. 473.

† Blondlot, *Essai sur les fonctions du foie*, Paris and Nancy, 1846, p. 62.

‡ Claude Bernard, *Leçons &c. liquides de l'organisme*, Paris. 1859, t. ii. p. 202.

§ The same year that Bidder and Schmidt's book was published, C. G. Lehmann expressed the opinion that more bile ought to be secreted 10 hours after food than 5 hours after; because there is more change in the blood later than earlier. (*Journal de Pharm. et de Chimie*, 1852, t. xxi. p. 399.)

sinks; and in 24 hours after the meal, it has fallen below the amount which it showed immediately after the taking of food.*

Arnold states that he found the greatest amount of bile always to make its appearance in the first hours after the meal had been taken. The figures which he gives are as follows:†

1 hour	5.257 grammes.
2 hours	5.346 „
3 „	5.121 „
4 „	4.612 „
5 „	4.146 „
6 „	3.504 „
7 „	3.583 „
8 „	3.817 „
9 „	4.344 „
10 „	4.012 „
11 „	3.612 „

Arnold's experiments were made on one dog, and there appear to have been only two sets of observations on this point.

Kölliker and Müller find that a very small amount of bile is secreted in the first and second hour after food. Sometimes the amount is even less than in the 19th to 25th hour. In the 3rd to 5th hour, they found almost without exception an increase of the secretion. Indeed in two cases the fifth hour showed the highest amount, while in the others the *maximum* was seen from the 6th to 8th hour. After this, the amount again fell until the *minimum* was reached in the 19th to 25th hour.‡

* Bidder and Schmidt, *Die Verdauungssäfte*, Mitau and Leipzig, 1852, p. 144.

† Friedrich Arnold, *Zur Physiologie der Galle*, Mannheim, 1854, p. 16.

‡ Kölliker and Müller, *Verhandlungen der phys.-med. Gesellschaft in Würzburg*, 1856, Bd. vi. p. 454.

Hour after food.	1st DOG.		2nd DOG		3rd DOG				5th DOG.	
	Bile.		Bile.		1st Series.		2nd Series.		Bile.	
	Liquid	Solid	Liquid	Solid	Liquid	Solid	Liquid	Solid	Liquid	Solid
1—2	1.450	0.051	1.221	0.040	0.823	0.035	0.675	0.026	1.538	0.053
3—5	1.407	0.047	1.462	0.042	1.198	0.044	0.986	0.034	2.222	0.060
6—8	1.514	0.048	1.705	0.046	1.242	0.047	1.093	0.035	1.889	0.054
9—14									1.368	0.041
15—18									1.435	0.043
15—20					1.085	0.040				
16—22	1.320	0.051								
19—21			1.119	0.036						
20—24									1.203	0.047
21—25							0.750	0.030		

The figures are grammes.

These observations of Kölliker and Müller seem to be certainly more worthy of confidence than those which went before them. They were made on the same animals, not as in Bidder and Schmidt's cases, on different animals at different times of digestion.

Voit, without giving further details, says that the observations, which he had made upon Bischoff's dog with a biliary fistula, showed that the secretion of bile rose immediately after taking nourishment. The *maximum* arrived in 2 to 4 hours. The solids of the bile were increased as well as the fluid part.*

In guinea pigs, it was noted by Heidenhain that no such great increase of the flow of bile took place after food. Nor did the flow seem much decreased by fasting. It was only when the guinea pig had fasted for 66 hours that any decrease was noted. The guinea pig is a vegetable eater, and his stomach remains full of food long after the last meal: so the process of diges-

* Karl Voit, *Phys.-chem. Untersuchungen*, Augsburg, 1857, p. 41.

tion is always going on, and in this way Heidenhain explains the difference between flesh eaters and vegetable eaters.*

Some experiments of Ritter's are an attempt to reconcile the varying statements of other observers. He made six observations on his dog and gives the following as the result of his labours on this point: that after food there are two *maxima* of secretion of bile; the former of these falls in the first or second hour after the meal; the latter has no such precise time of appearance; the less the amount of nourishment, the earlier its appearance; the greater, the later.†

Influence of the amount of food on the bile.—It has been seen that Kölliker and Müller found the amount of bile to fall to its lowest point, 19 to 25 hours after a meal; Bidder and Schmidt saw that by withholding nourishment from cats the amount of bile sank to a *minimum*;‡ 240 hours after the last meal, the amount of fluid bile was only 94 milligrammes in an hour, and of solid bile but seven milligrammes.

The Edinburgh Committee saw a marked effect follow the withholding of food from a dog. Only liver was given as food, and no water; the amount of bile fell to 104·8 grammes in the 24 hours against 140 grammes for the two foregoing days. The bile solids, however, rose to 7·73 grammes, about one half more than they had been; and this was due to a great rise in the organic constituents of the bile as the inorganic salts remained the same in amount. The next day, only water was allowed, and the amount of fluid bile fell to 41·6 grammes, and the solids to 2·77 grammes.§

From these observations it may be looked upon as a

* Friedländer and Barisch, *Arch. f. Anat. Phys.* 1860, p. 654.

† Joseph Franz Ritter, *Einige Versuche über die Abhängigkeit d. Absonderungs-Grosse der Galle von der Nahrung*, Diss. Inaug. Marburg, 1862, p. 27.

‡ Bidder and Schmidt, *op. cit.* p. 144.

§ Edinburgh Committee, *op. cit.* p. 222.

probable opinion that the withholding of food decreases the amount of fluid bile secreted, and possibly also of the solid bile.

Bidder and Schmidt also fed two cats abundantly with meat; one took in four days no less than a half of its own weight; the other took one-third of its own weight in two days. The amount of bile secreted by each animal was almost the same. For every kilogramme of cat, there was secreted in one hour, in the first cat, 2.055 grm. of fluid bile with .172 grm. of solids, and in the second cat 1.965 of fluid bile with .178 grm. of solids. The average which they give for cats is that one kilogramme secretes in every hour .608 grm. of fluid bile with 34 milligrammes of solids. So that if these two experiments on cats represent a general rule, a great increase in the secretion of bile takes place on an abundant diet.

In Arnold's experiments, the dog, weighing 7.75 kilogrammes, was fed daily with 750 grm. of meat. The amount of bile daily secreted was on an average 90.295 grm. One kilogramme of the dog, therefore, on this diet of meat secreted 11.65 grm. of bile in the 24 hours. One gramme of bile was secreted in twenty-four hours for every 8.306 gramme of meat given. When the same dog was daily fed on 470 grm. of rye bread, the weight of the dog being 7.812 kilogramme, there was secreted of bile on an average 63.024 grm. Therefore on this amount of rye bread one kilogramme of the dog secreted 8.067 grm. in the 24 hours. One gramme of bile was secreted in the twenty-four hours for every 7.459 gramme of bread given.*

The following table has been drawn up by Kölliker and Müller and is a convenient summary of what was done by these observers and those who had gone before them, of the amount of bile secreted under differing

* Friedrich Arnold, *Zur Physiologie der Galle*, Mannheim, 1854, p. 16.

Name of Observer.	For every kilo- gramme of dog there was secret- ed in 24 hours :		Food for every kilogramme of weight.	For every 100 grammes of food in the 24 hours there was se- creted of	
	Fluid	Solid		Fluid	Solid
	Bile	Bile		Bile	Bile
	Grammes.		Grammes.	Grammes.	
1. Nasse.	19'2	0'685	155 flesh meat	12'3	0'440
2. "	22'8	0'700	208 " "	11'01	0'337
3. "	23'1	0'784	260 " "	8'9	0'300
4. "	24'0	0'765	meat <i>ad lib.</i>	—	—
5. "	28'4	0'760	" " "	—	—
6. Arnold.	11'6	0'373	75 flesh meat	12'0	0'385
7. Kölliker & Müller.	32'7	1'034	—	—	—
8. " "	32'6	1'290	98 flesh meat	—	—
9. " "	26'1	1'013	92 " "	28'56	1'094
10. " "	21'5	0'748	94 " "	22'85	0'792
11. " "	36'1	1'162	64 " "	56'50	1'816
12. " "	53'6	1'683	94 " "	56'7	1'79
13. Bidder & Schmidt.	15'9	0'840	{ 32 " "	49'3	2'608
14. " "	16'7	0'696	{ 1'7 fat "	83'5	3'48
15. " "	24'5	1'176	{ 17 flesh	25'7	1'23
16. " "	28'7	1'268	{ 7'8 milk	35'1	1'54
17. Nasse.	17'7	0'446	{ 79 flesh	—	—
18. "	17'9	0'400	{ 8 bread	—	—
19. "	12'2	0'505	{ 66 flesh	—	—
20. Arnold.	8'1	0'215	{ 8 bread	—	—
21. Kölliker & Müller.	32'1	—	{ 100 flesh	—	—
22. Carl Voit.	11'8	0'503	{ 100 bread	—	—
23. " "	10'8	0'5	{ 130 flesh	—	—
24. Dr. George Scott.	23'1	1'13	{ 100 bread	—	—
25. Ritter.	18'75	—	87 " "	13'9	0'575
26. "	17'5	—	60 " "	13'4	0'353
27. "	15'2	—	{ 37'9 bread	—	—
28. "	13'4	—	{ 94 c.c. milk	—	—
29. "	10'5	—	48'2 flesh	24'5	1'115
30. Edinburgh Com- mittee.	6'47	0'412	54 " "	20'0	0'914
31. " "	7'82	0'28	{ 62'7 flesh	10'22	—
32. " "	5'27	0'34	{ 70 milk	10'29	—
33. " "	5'47	0'293	183'4 flesh	11'007	—
34. " "	3'53	0'146	170'6 " "	13'10	—
35. " "	21'8	0'801	138'8 " "	14'81	—
36. " "	4'64	0'23	103'5 " "	52'18	3'32
37. " "	9'24	0'305	70'5 " "	57'21	2'05
			12'3 dry food	58'9	3'165
			13'6 " "	40'13	2'148
			6'7 " "	92'9	3'49
			10'9 " "	23'99	1'21
			8'8 " "	51'84	1'714
			23'4 " "		
			19'34 " "		
			9'3 " "		

amounts of food.* The figures of the authors since 1856 have been put together for this work.

Kölliker and Müller say very truly that on first looking through this table it does not seem possible to draw any general conclusions from it. They think that there is a certain correspondence, however, between the conclusions of Nasse and Arnold on the one side; and Bidder and Schmidt with Kölliker and Müller on the other. The two first authors find the amount of solid bile secreted by one kilogramme of dog in 24 hours, on different kinds of food, to vary between 0.215 and 0.785 grm.; the latter observers find it between 0.696 and 1.290 grm. If, however, the amount of fluid bile secreted in the 24 hours for every kilogramme of dog be compared, a different aspect is given to matters; Nasse gives it as from 12.2 to 28.4 grm.; and Bidder and Schmidt between 15.9 and 28.7: a close correspondence. But the solid bile is that which is of most importance; and the higher figures of Nasse correspond to a higher amount of food, while the dogs of Bidder and Schmidt were fed rather low. The dogs of Kölliker and Müller were, however, better fed than those of Bidder and Schmidt, yet the amount of dry bile in Bidder and Schmidt's dogs was nearly on a level with Kölliker and Müller's. It would follow that the observations of these four writers have a real correspondence with each other. This is still more marked, as is also the agreement between Arnold and Nasse, when the amount of bile secreted for each 100 grm. of food is considered. Nasse and Arnold give between 8.9 and 13.9 grm. of fluid bile with 0.300 to 0.575 dry bile for every 100 grm. of food. Bidder and Schmidt with Kölliker and Müller on the other hand give much higher figures: 22.85 to 83.5 grm. of fluid bile with 0.792 to 3.48 of dry bile to every 100 grm. of food.

* Kölliker and Müller, *Verhandlungen d. phys. med. Gesellschaft in Würzburg*, 1856, Bd. vj. p. 461.

I am more inclined myself to agree with the first paragraph of Kölliker and Müller's argument, and to think that but few general conclusions can be drawn from this table, even if the more recent observations be taken into the service. The variations in the figures of the Edinburgh Committee are very considerable; a large amount of bile was secreted when either little or much food was given.

Ritter, a pupil of Nasse, made under his guidance many careful and interesting observations on a dog, in whom he had established a biliary fistula. He found that by decreasing the daily amount of food, the amount of bile also decreased.* For example: the dog, fed on 2500 grm. of meat daily, produced on an average 255.5 grm. of bile in the 24 hours. Fed only on 1000 grm. of meat daily, he produced 147.1 grm. of bile in the 24 hours. The following table shows the exact figures:

WEIGHT OF DOG BEFORE THE BILIARY FISTULA WAS ESTABLISHED = 13.5 KILOGRAMMES.

Series of experiments.	Food in fresh meat.	Average weight of animal.	Average amount of bile in 24 hours.	Average secretion of 1 kilogramme in 24 hours.	Amount of food in meat for every kilogramme of the dog in 24 hours.	For every kilogramme of meat there were secreted in 24 hours, of bile.
1.	2500	13.629	255.5	18.75	183.4	102.2
2.	2500	14.656	257.3	17.5	170.6	102.9
3.	2000	14.52	220.15	15.2	138.8	110.07
4.	1500	14.544	196.5	13.4	103.5	131.0
5.	1000	14.175	148.1	10.5	70.5	148.1

The weights in this table are in grammes.

The first series of experiments lasted uninterruptedly for 7 days: the second for 8 days: the third for 5 days: the fourth also for 5 days, but with an interlude of 3

* Joseph Franz Ritter, *Einige Versuche über die Abhängigkeit der Absonderung Grösse der Galle von der Nahrung*, Diss. Inaug. Marburg, 1862, pp. 10, et seqq.

days between the 2nd and 3rd day of observation; the fifth for 4 days without interruption.

Influence of the kind of food upon the secretion of the bile.—Bidder and Schmidt fed two cats only on fat or oil for five or three days, and a third was fed abundantly for several days on very fat meat. The first cat yielded by kilogramme in an hour 0·688 to 0·128 gm. of liquid bile, and 62 to 16 milligrammes of solid bile; the second, 0·347 to 0·211 gm. of fluid and 39 to 15 milligrammes of solid bile. The third cat, fed on very fat meat, yielded 0·327 to 0·181 gm. of fluid bile and 28 to 16 milligrammes of solid bile.* These figures are very little above, if not equal to, those given by cats who had fasted for days. It follows that, in animals fed solely on fat, the secretion of bile falls to a *minimum*. These observers also noted that those animals, with little fat under their skin, often gave a more abundant secretion of bile than fat ones.†

Yet, according to some experiments of Nasse, it would seem that if fat be added to the ordinary food, the amount of bile secreted is raised. For five days he fed a dog with meat and fat, and the secretion attained the amount of 219·8 gm. in 24 hours. The same amount of meat, but without the fat, was given for the five following days, and the secretion fell to 59·26 in the 24 hours. Then he gave fat, as much as the animal would take with the other food, for four days; and the amount of bile rose again to 206·13 in the 24 hours. The bile soon after fell again in amount, as the creature lost its appetite and refused its food.‡ The dog was therefore probably out of health during the observations.

Ritter has continued some observations in the same

* Bidder and Schmidt, *op. cit.* p. 148.

† p. 236.

‡ Hermann Nasse, *Commentatio de bilis quotidie a cane secreta copia et indole*, Marburg, 1851, p. 14.

direction, but without the striking results obtained by Nasse. He did not, however, feed his animal for several days without or with fat: but gave fat about every alternate day. There is but little variation in the amount.*

DATE.	FOOD.	GRAMMES OF BILE IN 24 HOURS.
Dec. 26.	1000 grm. of meat without fat.	170·3
27.	same with 125 grm. of hog's-fat.	213 grm.
28.	same.	212·3
Jan. 11.	1500 grm. of meat without fat.	182·6
12.	same.	207·2
13.	same with 125 grm. of hog's-fat.	180
14.	same.	202·8
15.	same without fat.	216·8
16.	750 grm. meat without fat.	171·0
17.	same.	162·8
18.	same.	124·1
19.	same with 125 grm. of hog's-fat.	132·0
20.	same.	138·6
21.	same without fat.	130·6
22.	same.	123·6

The belief that fat joined to other food causes an increase of bile is not supported by these figures.

The last experiments made by Ritter were the substitution of potatoes for flesh in the diet of his dog; the amount of bile at once sank and continued low, whether fat were or were not given with the potatoes. The amount of bile secreted in the twenty-four hours varied in four experiments from 46 to 66·1 grm.†

The observations of Arnold, who found a lower amount of bile secreted when the dog was fed on rye bread than when fed on meat, have already been quoted. The proportion for each kilogramme was 11·65 grm. of bile on flesh, to 8·667 on bread,‡ a considerable decrease.

* Ritter, *Einige Versuche über die Absonderungs-Grösse der Galle von der Nahrung*, Diss. Inaug. Marburg, 1862, p. 28.

† Ritter, *op. cit.* p. 32.

‡ Arnold, *Zur Physiologie der Galle*, Mannheim, 1854, p. 16.

And Karl Voit found about the same amount as Arnold when his two dogs were fed only on meat; 11.77 and 10.77 grm. of bile secreted by the kilogramme in the 24 hours.*

If the figures of Ritter be looked through, it is evident that most bile was secreted when the animal was most abundantly supplied with flesh. He does not seem to have tried feeding the animal with an equal weight of bread. When fed with potatoes in weight equal to that of meat, the secretion certainly fell very much lower (4: 1).

In looking at the table from Kölliker and Müller, it is hardly possible to draw any conclusion; if anything, the figures would seem to show that as much solid bile is secreted on a low diet as on a full one. The highest amount of solid bile secreted was when the dog was fed on but 17 grm. of meat, and 7.8 of milk for every kilogramme.

It would seem *à priori* probable that more bile should be secreted on a high than a low diet, and also that a nitrogenous diet should favour the secretion, as the bile acids contain so much nitrogen. The whole of Ritter's experiments are rendered much less valuable by his neglect of the solid constituents of the bile; a troublesome estimation, it will be owned, but one which cannot be avoided in investigations of this sort.

Difference between night and day.—Westphalen noted in his patient that the lowest amount of fluid bile in the twenty hours was always secreted in the night, between 2 and 6 a.m. It contained, however, a far larger percentage of solids.† Nasse had before remarked that in the dog the amount of bile was less at night than in the day, although if the dog were fed night and morning instead of at mid-day, or had taken a great quantity of

* Karl Voit, *Phys.-Chem. Untersuchungen*, Augsburg, 1857, pp. 38 and 40.

† Westphalen, *Deutsches Arch. f. klin. Med.* 1873, Bd. xi. p. 595.

food, this decrease was not noticed. During the night it appears that the percentage of solid matters was usually greater than during the day.* Ritter, Nasse's pupil, repeated this observation in 1862.†

Influence of drink on the secretion of the bile.—In Westphalen's patient no increase in the bile followed the drinking of a considerable quantity of water on two following days. There was no noteworthy dilution of the secretion, although the amount of urine was doubled, and its specific gravity sank from 1021 to 1011.‡ On animals, however, quite the opposite has been seen. Bidder and Schmidt noted that in three dogs the amount of bile was doubled or trebled very shortly after drink was given; not merely the water but the solid contents of the bile were increased.§ In one dog, however, this result did not always take place; for out of five experiments it was not seen in two and but slightly in one.||

Nasse reports shortly that if the dog took a great quantity of water with the food, there was a larger secretion of bile.¶ Arnold says the same thing.**

Röhrig also found, both in dogs and rabbits, that the injection of warm water into the small intestine had a marked effect on the amount of secretion. The effects of a second injection were more lasting than of the first.†† Only the amount of bile was estimated in Röhrig's experiments, not the solid contents.

Mosler injected water into the veins, but no account is given of the amount of the secretion if increased or decreased.‡‡

* Nasse, *Comment de bilis quotidie, etc.* Marburg, 1851, p. 19.

† Ritter, *Einige Versuche u. s. w.* Diss. Inaug. Marburg, 1862, p. 23.

‡ Westphalen, *Deutsches Arch. f. klin. Med.* 1873, Bd. xi. p. 600.

§ Bidder and Schmidt, *op. cit.* pp. 166 and 168.

|| p. 181.

¶ H. Nasse, *Commentatio de bilis quotidie, etc.* p. 18.

** F. Arnold, *Zur Physiologie der Galle*, Mannheim, 1854, p. 17.

†† Röhrig, *Stricker's Med. Jahrb.* Wien, 1873. p. 246.

‡‡ Mosler, *Arch. f. path. Anat.* 1858, Bd. xiii. p. 32.

Prince Tarchanoff injected 200 C.C. of distilled water into the jugular vein of a dog and found a great increase in the amount of fluid bile and of the pigment.*

Socoloff, in two experiments also made in Hoppe-Seyler's laboratory, came to results which agree with those of Westphalen rather than with those of Bidder and Schmidt and the other observers. He injected 50 C.C. of 1 *per cent.* solution of common salt into the stomach of a dog, and 100 C.C. of a like solution into the crural, later on. Rather a fall than an increase was noted, especially in the second case, both in the amount of fluid and solid bile.†

Heidenhain agrees with Bidder and Schmidt that an increase of bile takes place in most cases; but not in all. Out of ten there were two in which no increase of the flow took place.‡

Influence of an increase or decrease of the blood pressure in the liver on the secretion of bile.—Heidenhain, with the assistance of his two pupils, Körner and Strube, found that the sudden raising of the blood pressure by injecting $\frac{1}{20}$ or $\frac{1}{40}$ of their weight of water into the veins of guinea pigs, caused in the first hour a decrease in the amount of bile. The decrease was always present in the first hour, and in 4 of the 7 experiments lasted for some hours, while in three experiments it soon began to rise again. In these four experiments the fall was considerable; it was smaller in the last three.

On lowering the blood pressure by bleeding the guinea pig, or by tying one of the mesenteric veins or the splenic vein, there followed a like decrease in the amount of bile collected.§

* Johannes, Fürst Tarchanoff, *Arch. f. d. ges. Phys.* 1874, Bd. ix. p. 330.

† Socoloff, *Arch. f. d. ges. Phys.* 1875. Bd. xi. p. 176.

‡ Körner and Strube, *Studien d. phys. Inst. zu Breslau*, Leipzig, 1863, Heft ii. p. 94.

§ Heidenhain, *Studien d. phys. Instit. zu Breslau*, Leipzig, 1863, Heft ii. p. 94, Cf. below (p. 122.) the important experiments on irritation of the spinal chord, and consequent changes in the blood pressure in the liver.

Hermann Nasse says that no change in the secretion of the bile followed the loss of a "few ounces" of blood from the jugular vein.*

Johannes Ranke found that the secretion of bile in a guinea pig absolutely stopped when the creature had lost $\frac{1}{3}$ of the weight of its blood.† He also says that the secretion begins again if fluids be injected into the veins after this loss of blood.‡ Röhrig found the secretion of bile in two dogs to be brought to an end by a bleeding; the injection of water into a mesenteric vein again made the secretion to flow, but only for a very few seconds.§

Influence of the contractions of muscles on the secretion of bile.—The relation of bodily exercise, or of the contraction of muscles, to the metamorphoses of the tissues is one of the most interesting problems in physiology. Johannes Ranke has attempted to make out the influence of muscular contraction on the bile, and comes to the conclusion that the change in the distribution of blood to the muscles corresponds to a change in the functions of the liver; and that when the muscles from their contraction contain more blood, less blood flows to the liver, which therefore does less work; thus the muscular contraction has all the effect of bleeding.|| Johannes Ranke's experiments seem somewhat open to criticism. The intestines were considerably interfered with, and a disturbance in the circulation might thus be readily set up. And the application of the electricity seems to have followed at very short intervals, so that it would be hard to distinguish between

* Hermann Nasse, *Commentatio de bilis quotidie a cane secreta copia et indole*. Marburgi, 1851, p. 12.

† Johannes Ranke, *Die Blutvertheilung*, Leipzig, 1871, p. 190.

‡ p. 117.

§ Röhrig, *Stricker's Med. Jahrb.* Wien, 1873, p. 246.

|| Johannes Ranke, *op. cit.* p. 117.

the effects of the contraction and exhaustion of the muscles.

Inspiratory movements and struggles are noted by many writers as causing an increased flow of bile from a biliary fistula: so vomiting. These phænomena are not due to an increased secretion, but, the pressure within the belly being raised, the bile already secreted and in the ducts is expelled. The Edinburgh Committee noted an increased flow of bile during the first half hour that the dogs were taken from their cages and let run about.*

Influence of the nerves on the secretion of bile.—Schiff divided in dogs and cats the nerves which accompany the hepatic artery, but found no change in the secretion of bile.† Röhrig found no change on division or irritation of the *vagus*.‡

Heidenhain's pupils, Goldschmidt, Hausmann and Lissa, found that in guinea pigs a considerable decrease in the secretion of bile followed the section of one or both *vagi*. But the disturbances which section of the *vagus* sets up are many. One of them is a very slow breathing; and it was found that when artificial respiration was used the amount of bile evacuated by the fistula at once rose, but not quite to the normal amount. If, however, only one *vagus* be divided, it is sometimes long before the slow breathing appears. In two cases this was noted; in one of these the amount of bile was unchanged; in the other it sank somewhat. But little can be inferred from these experiments; and it was next determined to divide the *vagi* below the diaphragm, after the branches to the lungs had been

* Edinburgh Committee, *Report of the Thirty-eighth Meeting of the British Association for the Advancement of Science; held at Norwich in Aug. 1868.* Lond. 1869, p. 231.

† Schiff, *Canstatt's Jahresbericht f. 1862*, Bd. i. p. 126, quoted from *Schweizerische Zeitschrift f. Heilkunde*, 1862, Bd. i. 1862, p. 1.

‡ Röhrig, *Stricker's Med. Jahrb.*, 1873, p. 258.

given off, and to irritate the nerves below the diaphragm. In making the biliary fistula a ligature was placed on the gullet below the diaphragm, so that the *vagi* could readily be compressed. The amount of bile fell, but not very markedly. Electrical irritation of the *vagi* was followed by no remarkable increase in the amount of the secretion of the bile. It may be concluded that the *vagi* have no immediate influence on the bile; but the changes which are seen are due to slow breathing, drawing of blood from the liver into the chest, decrease of movement in the portal system, or increase of the heart's action, all of which tend to beget a passive congestion of the liver.*

Pflüger, without giving details, shortly reports that he has cut through the *vagi*, phrenics, splanchnics, and sympathetics, has destroyed the celiac plexus, has crushed all the nerves entering the porta, and yet found the secretion of the bile to continue as before. From this he draws the inference that the liver possesses a nerve centre within itself. Irritation of the *vagi*, splanchnics, celiac plexus, and the portal nerves, gave no result. If the liver itself be irritated with electricity for one or two minutes, the flow of bile becomes very slow, or even leaves off altogether, for as much as 10 to 20 minutes. Pflüger thinks that this appearance cannot be explained by supposing a contraction of the vessels or bile ducts.†

Some very interesting experiments were also made by Freundt and Graue in Heidenhain's laboratory; they found no change in the amount of fluid bile or bile solids after the diabetic puncture had been made on 9 guinea pigs.‡

* Heidenhain, *Studien d. phys. Instituts zu Breslau*, Leipzig, 1863, Heft. ii. p. 82.

† Pflüger, *Arch. f. d. ges. Phys.* 1869, Bd. ij. p. 191. Pflüger ends his paper with the words: "Bald Ausführlicheres," but I do not know of any paper published afterwards in which the details necessary for forming a judgment on the results are given.

‡ Heidenhain, *op. cit.* p. 69.

Heidenhain and his pupils found that, on irritating the spinal chord at the level of the third or fourth cervical vertebræ, the amount of bile was decreased. In the one experiment given to us as a specimen, the bile was reduced almost one half. The spinal chord was irritated by needles inserted into the neck, along which electricity was sent by means of a magnet electromotor. The animal showed several contractions of the muscles during the time of irritation. But if these observations be looked at a little attentively, it is seen that there were two periods; one, at the very beginning of the irritation, in which the secretion seemed hastened; and a second, following the first, in which the secretion was decreased. Casting about for an explanation of these two appearances, it seemed to Heidenhain that the first might be explained by supposing an increased flow of bile, a mere driving out of material already formed; and the second, by supposing a narrowing of the intralobular ducts, which would thus cause a hindrance to the descent of bile formed. Or, as the branches of the mesenteric and hepatic arteries contract forcibly when the spinal chord is irritated, it might be that the blood pressure in the capillaries of the liver would sink, and thus a true decrease of the secretion of bile take place.

In deciding between these two hypotheses it must be considered that if there be a narrowing or contraction of the gall ducts, there would be no tendency of fluid to flow back into the liver, when a tube filled with fluid is connected with the common duct, and the tube placed horizontally, either on a level with the duct, or but slightly above it, so as to exert but small pressure. During the first period of irritation of the spinal chord, the fluid in the tube remained either stationary, or was pushed somewhat forward. During the second period, the fluid ran back into the liver: so that the hypothe-

sis of a contraction of the ducts had to be given up. Now this flowing back of the bile into the liver might be due to three things: (i.) a decrease of secretion; (ii.) an increase of absorption; or (iii.) a combination of both these circumstances. The bile, however, runs back too rapidly for the appearance to be due solely to a decrease of the secretion only. It must therefore be an increase of absorption. To what is this increase of absorption due? Heidenhain answers: to a decrease of the blood pressure in the capillaries of the liver, and points out that Frerichs had already formulated such a theory of jaundice.* Heidenhain brings forward experiments made by his own pupils, Kube and Szostokowski, which show that, after a general bleeding, the bile is readily absorbed by the gall ducts. By again injecting blood into the veins, the absorption becomes less. Max Heidenhain and Lichtheim, also, lowered the blood pressure in the liver by compressing the aorta in rabbits after the arteries to the head had been given off, and found the same result. With compression, the bile was absorbed; during the intervals of compression, it flowed out of the ducts.† The likeness of the states caused by irritation of the spinal cord, and by mechanically inducing a lowering of the blood pressure in the liver is thus manifest. The contraction of the small arteries is a necessary part of both. Kube and Szostakowski have also made experiments in which they estimated the blood pressure in the carotid at the same time that they noted the changes in the flow of bile. They found the flow of bile to decrease only when a great increase of pressure was seen in the large arteries; that is, when the smaller arteries were contracted, and therefore, the pressure in the capillaries was small.

* Frerichs, *Klinik d. Leberkrankheiten*, Braunschweig, 1858, Bd. i. p. 89-94.

† See Ranke's experiments above, p. 119.

The appearance of an increase in the flow of bile, during the first period of irritation of the spinal chord, Heidenhain finds it more difficult to explain. He falls back upon his old belief in a contractility of the gall ducts. He does not believe that there is any increase of secretion, but the appearances seen in his experiments rather suggest that the secretion already formed is shot out of the ducts during the first period. Then he gives histological reasons for thinking that the gall ducts contain contractile elements.* Another motive is the irregularity of the appearance of the secretion which may often be noted in animals left to themselves. Heidenhain ends his paper by the notes of another experiment on compression of the aorta and outflow of bile. The flow of bile was great during the time of compression. Heidenhain sets this down to the contractility of the gall ducts, because the muscular coat of the bowels and the uterus contract under like circumstances.†

Another explanation of this first period may be given. The blood vessels and gall ducts lie close together in the portal spaces in the liver. Any increase in the one must cause a decrease in the size of the other. If, before the contraction of the small arteries begin, there be a dilatation of them, as seems quite likely, there will be a pressure exerted upon the ducts corresponding to the dilatation of the blood vessels. This would account at once for the apparent increase of the flow of bile, and for the appearance which Heidenhain has noted that it was, as it were, shot out of the ducts.

Röhrig in the course of his research, made an attempt to repeat Heidenhain's experiments on irritation of the spinal chord. He did not use the same method of

* For a discussion of this question and the neighbouring one of *icterus spasticus*, see the chapter in this work on *icterus simplex*.

† Heidenhain, *Studien des phys. Instituts zu Breslau*, Leipzig, 1868, Heft iv. pp. 226-246.

irritation, and it is plain therefore, that his results may not be compared with those of Heidenhain. In a dog and two rabbits, he irritated with electricity the crural and sciatic nerves, but he altogether missed the first stage of increased flow, and saw only the second stage, that of decreased flow.*

J. Munk has repeated these experiments, both in Heidenhain's way and in Röhrig's way, and comes to the conclusion that Heidenhain's observations are right, and that Röhrig is mistaken.†

Röhrig, being led to the assumption that hyperæmia of the bowels and liver corresponded to an increase in the activity of the liver, determined to watch the effect of cutting the splanchnic nerves. He only did this experiment twice; and this in two dogs already at the point of death from other experiments. The division of the nerves was followed by some increase in the amount of bile, but ceased in a few seconds with the life of the animal.‡

Munk repeated Röhrig's experiment of dividing the splanchnics in rabbits; and found that the flow of bile was first hastened, then made slower. Assuming that the splanchnics contain the greater part of the vaso-motor nerves of the liver, and also the nerves which, according to Heidenhain's belief, supply the muscular coat of the gall ducts, it would follow that after dividing the splanchnics, irritation of the spinal chord would not be followed by any change in the flow of bile. This assumption was verified by experiment. Reflex irritation of the spinal chord of a rabbit was set up by the irritation of the sciatic nerve; and as a consequence, first a quicker, and then a flow of bile slower than natural took place. The splanchnics were then divided,

* Röhrig, Stricker's *Med. Jahrb.* Wien, 1873, p. 259.

† J. Munk, *Arch. f. d. ges. Phys.* 1874, Bd. viii. p. 151.

‡ Röhrig, *op. cit.* pp. 257 and 258.

and the sciatic nerve again irritated, but no change in the flow of bile was noted.*

Röhrig found in two rabbits that division of the spinal chord high up in the neck was immediately followed by a great increase of the flow of bile, then a decrease, and the secretion finally ceased with the death of the animal. In a third rabbit, already used for other experiments of compression of the vessel, this method of death caused a slight increase in the flow.†

Influence of the ligature of certain vessels.—The effects of ligature of the portal vein or hepatic artery have already been discussed,‡ and Heidenhain's results after compressing or tying the aorta have been spoken of.§

Röhrig found that complete ligature of the aorta close to the diaphragm in a dog and a rabbit was followed at once by a decrease in the flow of bile. Digital compression did not give the same result. Ligature of the aorta, after the cœliac had been given off, caused at first a slight increase in the flow of bile which became weaker and weaker, as the place of ligature was moved farther down.

The same observer found that ligature, complete or incomplete, of the vena cava, at some point between the left auricle and the hepatic veins, caused a decrease if not a stoppage of the flow of bile.

Röhrig comes to the conclusion that the secretion of bile is not altogether dependent on the blood pressure in the liver. The blood pressure is increased when the aorta below the cœliac is tied, and yet there was a slight increase in the flow of bile; there was a complete stoppage of the flow when the blood pressure was raised by

* J. Munk, *Arch. f. d. ges. Phys.* 1874, Bd. viii. p. 160.

† Röhrig, *op. cit.* p. 258. The results of Röhrig's experiments are rendered much less valuable from a scientific point of view by his custom of using one animal for two experiments.

‡ See p. 87.

§ See p. 124.

tying the inferior cava.* It seems to me that the two experiments ought not to be compared.

Effects of irritation of the digestive canal.—Röhrig has irritated the mucous membrane of the mouth, tongue and stomach, of the duodenum and large and small intestines, the peritonæum, by means of ammonia and acetic acid, and weak or strong electrical currents, and yet seen no change in the flow of bile. In a few experiments he thought that dropping a little ammonia on the tongue, or pinching it with a forceps, called forth a momentary increase. He has never, however, seen the least change, with any agent, follow irritation of the duodenum: acetic acid, dilute hydrochloric or sulphuric acid.† It should be remembered that Claude Bernard noted that if the orifice of the bile duct into the duodenum were touched with weak acetic acid, immediately a rush of bile poured into the intestine. Nothing of the sort, however, happened if instead of acetic acid, a slightly alkaline fluid were used, as for example, carbonate of soda.‡ Now Tiedemann and Gmelin always found the gall bladder empty in animals during digestion, and they explain this on the theory of an irritation of the duodenum by the chyme. No doubt they are right in this view. The acid chyme, passing over the papilla, causes a flow of bile as in Bernard's experiment.

Röhrig injected the contents of the stomach and small intestine of a dog, who had been well fed, into the stomach of another dog. There was a much greater increase in the amount of bile than when mere water was injected. A result that might be expected.

* Röhrig, Stricker's *Med. Jahrb.* Wien, 1873, p. 243.

† Röhrig, *ibid.* p. 248.

‡ Claude Bernard, *Leçons de physiologie expérimentale*, Paris, 1856, t. ij. p. 429. This experiment has been repeated and confirmed by Kütke (*Zur Function der Leber*, in Heynsius' *Studien des. phys. Inst. zu Amsterdam*, Leipzig and Heidelberg, 1861, p. 38.) Cf. Tiedemann and Gmelin, *Recherches*, etc. Paris, 1827, partie i. p. 375.

He found that during diarrhœa the flow of bile was very abundant.* The exposure of the intestines to the air was also followed by some increase of the secretion.

H. Nasse, however, had noted in 1847 that in diarrhœa the amount of bile was decreased,† and the Edinburgh Committee,‡ in 1868, and Dr. Rutherford later on, after Röhrig's experiments, did not find that active purging increased the secretion of bile. "Whether or not," says Dr. Rutherford, "the depressing effect on the liver is due to the tendency towards collapse that results from violent purgation, or to the abundant abstraction of certain matters from the portal vein, is doubtful. The point, however, is one of such importance that it demands further investigation.§"

In disease.—H. Nasse noted that if his dog became feverish, the amount of bile was decreased.||

Pressure under which the bile is secreted.—Heidenhain, and his pupils, Friedländer and Barisch, found that when a manometer was connected with the gall bladder of a guinea pig, in whom a biliary fistula had been made, the bile or water of the manometer rarely rose above 200 millimeters in height. After reaching this height it remained tolerably constant. The bile is therefore secreted at the small pressure of 200 mm. of water pressure.¶ Kowalewsky finds that in woorarised cats, the pressure is not constant, but liable to variations, from 12 to 20 mm. of mercury. These variations depend chiefly upon the variations in the arterial

* Röhrig, Strecker's *Med. Jahrb.* Wien, 1873, p. 248.

† H. Nasse, *Commentatio de bilis quotidie*, etc. p. 19.

‡ Edinburgh Committee, *Report of the Thirty-eighth Meeting of the British Association for the Advancement of Science; held at Norwich, August, 1868*, Lond. 1869, p. 229.

§ Rutherford and Vignal, *Experiments on the Biliary Secretion of the Dog*, p. 17: Report attached to the *Brit. Med. Journal*, Vol. ii. 1876.

|| H. Nasse, *Commentatio de bilis quotidie*, etc. Marburg, 1851, p. 19.

¶ Friedländer and Barisch, *Arch. f. Anat. Phys.* 1860, p. 659.

pressure. The pressure under which the bile is secreted rises with the rise of the blood pressure. The change is not immediate, but needs some time before it be brought about, due doubtless to some changes going on either in the secretion of the bile or absorption from the ducts. The resistance to the passage of the bile into the bowel also varies in the same species. For example, in woorarised cats it varies from 3·4 to 7·5 mm. of mercury. The bile will thus be stopped entering the duodenum if a resistance of only 3·4 to 7·5 mm. of mercury be opposed to it.*

Summary of Knowledge as to the Physiology of the Bile.

It is much to be regretted that the physiology of the bile is still in so unsatisfactory a state. Compared with it, the chemistry of this humour might almost be looked upon as a well-worked field, although physiological chemistry has made but small progress in what may really be called knowledge.

It is still uncertain if the liver be a mere filter, or if it secrete the bile itself, although the general belief of physiologists is in favour of the latter.

Of late years a belief in a kind of circulation of the bile has much prevailed; that is, that the bile is secreted by the liver, passed into the intestines, absorbed by the intestines, passed into the blood, and again brought back by the blood to the liver to be again excreted.

It is also thought that the bile pigments are direct derivatives of the hæmoglobin of the blood corpuscles, though the evidence in favour of this has of late become weaker. The bile acids must be derived from some nitrogenous bodies, and it is therefore probable enough that they come from the albuminous compounds of the system, though whether the breaking down of the tissues or the splitting up of the peptones from the

* Kowalewsky, *Arch. f. d. ges. Phys.* 1874, Bd. viij. p. 597.

food furnish the bile acids is not known. It is doubtful if the cholestearin and lecithin be formed in the liver or are merely excreted from the blood. It would appear that a supply of blood from the hepatic artery is needful for the secretion of bile, as, if arterial blood be completely kept out of the liver, death of the liver takes place; but whether the portal vein only bring the materials of the bile is not known.

The amount of bile both in man and brutes secreted during the 24 hours is liable to very considerable fluctuations in health. In the few cases in which biliary fistulæ have been established in man, and the amount of bile estimated with care, the bile has varied from 7 to 22 ounces in the 24 hours. In the two instances in which the calculation has been made in man, one kilogramme has secreted 7.34 grm. and 14 grm. of fluid bile, and 0.166 grm. and 0.44 grm. of solid bile in the 24 hours. A glance at the table given by the Edinburgh Committee (see p. 104.) will show how much greater are the variations in dogs.

It would seem likely that the taking of food into the stomach is followed in an hour or two by an increased secretion of bile. In man, it seems doubtful if this be always the case. Perhaps this may be explained by the frequency with which meals are taken by man, by which the liver is being continually excited, and so feels less the stimulus of any one meal; while in dogs, which nature intended should be fed only once in the day, or less often than this, the liver feels the ingestion of a meal as a rare excitement.

During fasting the amount of bile is much decreased.

No definite relation has yet been discovered between the kind and amount of food, and the amount of bile.

During the night, especially after midnight, a less amount of bile is secreted; but it is more concentrated. Observers are much at variance whether drink increase

the amount of a diluted bile, as with the urine, or whether it have no influence on the bile, or whether the bile be decreased in amount. Some think that a greater amount of a highly pigmented bile follows the injection of water into the veins.

No nervous influence has yet been found directly to affect the secretion of bile. The diabetic puncture is followed by no change.

On lowering or raising the blood pressure in the liver, the amount of bile which escapes from a biliary fistula is decreased. It is probable that the decrease of bile seen during a low blood-pressure is due to the passing of the bile, already secreted, into the blood, and is not due to a real decrease of secretion.

Purging causes a decrease in the amount of bile secreted.

The bile is secreted in guinea-pigs and in cats at a very low pressure.

Irritation of the papilla in the duodenum, by an acid, is followed by a rush of bile into the duodenum. The acid chyme is therefore probably the natural irritant of the gall-bladder and ducts.

Vomiting is followed by an increased expulsion of bile; so also is muscular exercise.

CHAPTER VII.

THE OFFICE OF THE BILE.

It would seem necessary that a secretion, which is mixed with the food almost as soon as it leaves the stomach,* which is the product of the largest gland in the body, a secretion in the dog said to equal, in 24 hours, $\frac{1}{50}$ of his weight and of a rabbit $\frac{1}{8}$, should have some notable purpose in the animal œconomy. Yet physiologists have striven, and probably will strive, for many years over the uses of the bile. The same obscurity which hangs over the rest of the physiology of this humour envelopes to an equal, if not a greater, degree, the use to which it is designed by nature.

Is the bile an excrement only or not? It was taught by Aristotle that in animals the gall was an excrement and served no special purpose.† It is said also that Paracelsus considered the bile a useless humour and superfluous member of the animal œconomy.‡ In modern times the doctrine of Aristotle has been maintained, but not wholly, by Tiedemann and Gmelin,§ before Blondlot.

It might be thought this question of the excremental character of the bile would be settled by diverting the natural course of the bile from the intestine to the outside of the body. This was done by Schwann, who

* In omnibus animalibus bilis in principium intestini adfunditur, ut nihil fere alimenti ad sanguinem veniat, quod cum ea non mistum sit. (Haller, *Elem. Phys.* Lugd. Bat. 1764, t. vj. p. 615.)

† Aristotle, *On the parts of animals*, Book iv. Chapter ij. Taylor's ed. Lond. 1810, p. 113.

‡ Paracelsus, quoted by Eisenmann, *Die Krankheits-Familie Cholosis*, Erlangen, 1836, p. 13.

§ Tiedemann and Gmelin, *Recherches &c. sur la Digestion*, Paris, 1827, 2e Partie, p. 58.

devised a method of making such biliary fistulæ. His results were these: out of 18 dogs the common duct was re-established in 2, and in 10 death might be looked upon as the result of the operation. So that only six remain. They died in 7, 13, 17, 25, 64, and 80 days after the operation, with symptoms of inanition, loss of flesh, muscular weakness, unsteadiness of gait, and falling out of the hair. These symptoms were the more pronounced, the longer the animal lived. No difference was seen if the creature licked up the bile from the fistula, or if it were hindered from so doing. Schwann believes that the bile is not solely an excrement like the urine, but is essential to life; that, if it be diverted from the intestine, a loss of weight at once sets in, and that death will follow in 2. or 3. weeks, sometimes more, sometimes less.*

Blondlot, on the other hand, set up a biliary fistula in a dog; and after the first week or two, during which the animal was out of health, as it licked the bile from the wound, the dog regained its former state and its usual amount of fat. It ran about the house, and went for walks in the town and country, appearing to ail nothing. Blondlot concludes from this one experiment that the bile is of no use, but is simply an excrement.† Schwann later on repeated his experiments on thirty dogs. In the end, all died; but one lived a year, and another four months. Nasse kept a dog alive, with the weight tolerably the same, from the 12th of August in one year, to the 27th of January in the next.‡ The Edinburgh Committee kept in good health a dog with a biliary fistula

* Schwann, *Arch. f. Anat. Phys. u.s.w.* 1844, p. 127.

† Blondlot, *Essai sur les Fonctions du foie*, Paris and Nancy, 1846, pp. 55 *et seqq.* This dog of Blondlot's lived five years in perfect health, was active, used for hunting, and had pups every year. It died without apparent cause, and on dissection the obstruction of the ducts was found to be perfect. (See *Comptes rendus*, 1851, t. xxxii. p. 904.)

‡ Schwann and Nasse, quoted by Frerichs, Wagner's *Handwörterbuch d. Physiologie*, Braunschweig, 1846, Bd. iii. Abth. i. p. 837.

from April 24, 1868, to September 11 of the same year. It gained nearly 4 kilogrammes in weight during the five months that it lived without bile passing into the intestine; and had kept its strength, notwithstanding a partial poisoning with corrosive sublimate, purging with podophyllin, and dosing with taraxacum.* The Committee think that much depends on the health of the animal at the time that the biliary fistula is established. If the strength be good, health is usually preserved.

The observations of Bidder and Schmidt confirmed in all the more important particulars the results of Schwann. In their first experiment they found the dog to lose weight daily, although he was fed with four hundred grammes (nearly half a pound) of meat. His weight before the operation was six kilogrammes; after death at the end of a month, less than three and a half. Thus, the wasting of the animal was something very noteworthy. The skin was loose, the muscles scarcely to be felt, and the movements of the animal were very weak, although it was only on the day before its death that it did not leave its kennel. The hairs fell out in great abundance, leaving bald spots on the trunk and limbs. A great contrast to the miserable appearance, was the enormous appetite, of the creature. Digestion seemed to go on much as usual. The stools were not frequent, but were remarkable for their filthy smell; so also was the flatus which was passed by the animal almost incessantly. Much the same appearances were seen in their second experiment. In their third, the spleen was first removed and then a fistula set up. The dog lived two months and was killed. It showed the same great appetite, loss of flesh, and other symptoms that the others did; only it seemed to preserve its health.

* Edinburgh Committee, *Report of the Thirty-eighth Meeting of the British Association for the Advancement of Science; held at Norwich in August, 1868*, London, 1869, p. 231.

Bidder and Schmidt conclude that the question whether the bile be merely an excretion cannot be answered simply with yes or no.* In some cases it may be looked on as such, when the drain caused by the loss of bile can be fully covered by the increased amount of food taken; but in the greater number this compensation is not possible, and the loss becomes so great that life can no longer be kept up.

Is the bile needful for digestion in the stomach and intestines? Eaglesfield Smith found some advantage to the digestion in a case of jaundice in administering the bile of mammals. In Abyssinia and other uncivilised countries, he says, bile is thought to be a stomachic and a luxury;† he immersed flesh in gall for 14 hours at a heat equal to the human body, and found that it had lost half its weight; and he thinks therefore that bile is of great aid in digestion, due to its power of acting on grease.‡

In order to test this theory that the bile aided the formation of chyle, the first Sir Benjamin Brodie conceived the idea of tying the bile duct, and thus hindering the bile from passing into the intestine. He then watched the effect on the digestion. That in the stomach he found to continue as usual; but the conversion of chyme into chyle was invariably and completely interrupted: not the smallest trace of chyle was perceptible either in the intestines or in the lacteals.§

Magendie repeated Brodie's experiments in two animals, and found that white chyle was formed, together with fæces which resembled ordinary fæces

* Bidder and Schmidt, *Die Verdauungssaefte*, Mitau and Leipzig, 1852, pp. 98-114.

† Dr. George Harley says that bile is drunk with great glee by the Kaffres. (*Jaundice*, London, 1863, p. 18.)

‡ Eaglesfield Smith, *European Magazine*, 1797, Vol. xxxi. p. 386. Cf. *Observations and experiments on the digestive powers of the bile in animals*, Lond. 1805.

§ Brodie, *Quarterly Journal of Science*, 1823, Vol. xiv. p. 342.

save that they were white.* Tiedemann and Gmelin, however, found that while the liquid in the lacteals of dogs whose bile ducts had not been tied was whitish, it was without colour and clear in those in whom they had been tied; so also was the fluid in the thoracic duct. The difference is due to the absence of fatty particles which give a milky appearance to the fluid. The formation of chyle was not absolutely put an end to, as Brodie maintains, but that less fat was absorbed when the bile was hindered from passing into the duodenum.†

Bidder and Schmidt examined the chyle from the thoracic duct of dogs with biliary fistulæ; in no case did they find it white, but opalescent, transparent, now and then yellowish; it clotted as soon as taken from the duct. Of three cases, there were 55·26, 58·42, and 83·38 *pro mille* of solids, figures which are within the averages of health. The amount of fat in the chyle was, however, very small. The amount with ordinary nourishment in a healthy dog may be as high as 32 *pro mille*. In these it was under 2 *pro mille*.

Bidder and Schmidt also examined the fæces of animals in whom the bile was cut off from the intestine. They found that the albuminous bodies of the food had almost entirely disappeared from the fæces; so also had the starch, while a good part of the fats was also absorbed; one kilogramme of the animal taking 5·17 grm. of fat in the 24 hours.‡ Some part of the fat which is ordinarily absorbed is therefore not taken up when bile is not present.

Certain Chemical Properties of the Bile. These properties should have been discussed under the chapter on the chemistry of the bile; but it is more convenient

* Magendie, *Précis élém. de phys.* Paris, 1836, 4e éd. t. ij. p. 119, note.

† Tiedemann and Gmelin, *Recherches exp. etc. sur la Digestion*, Paris, 1827, 2e Partie, pp. 55 and 95.

‡ Bidder and Schmidt, *Die Verdauungssäfte*, Mitau and Leipzig, 1852, pp. 220-228.

to consider them at this point with the use of the bile in the digestion of aliments.

That bile has some power of emulsifying fats is well known from its domestic use. When shaken up with oil it forms an emulsion better than plain water, but not nearly so well as pancreatic juice. Dr. Bence Jones says that bile has no chemical action whatever on the neutral fats.* And in this Lenz† and others agree with him. Lenz says that if ox bile be mixed with an equal quantity of pure oleic acid, shaken together, and the whole kept at a temperature of 35° to 40° C. (95° to 104° F.) then three layers are formed; the uppermost contains pure oleic acid; the lowest pure bile; while the middle is of a whitish green colour and soluble in water. This can be again divided by hydrochloric acid into two layers, one of pure oleic acid, the other of chloride of sodium. So that it is the soda salts of the bile which form a soap with the fatty acids. Free fatty acids may be formed by the action of the pancreatic juice. But the greater part of the fat of the chyle is not soap, but finely-divided fat in minute drops and granules.

C. A. von Wistinghausen found that oil passed more readily through animal membranes moistened with bile than with water; and more readily at the temperature of the body than at a temperature of 19° C. Also that oil rose more readily in capillary tubes wetted with bile than in tubes that were dry or wetted with water.‡

Mr. Charles H. Williams has also made some careful investigations on this point in Professor Bowditch's

* Bence Jones, *Medical Times*, 1851, July 5, p. 3.

† Lenz, *de adipis concoctione et absorptione*, diss. inaug. Dorpati, 1850, quoted by Bidder and Schmidt, *op. cit.* p. 228.

‡ C. A. von Wistinghausen, *Experimenta quaedam endosmotica de bilis in absorptione adipum neutralium partibus*, Diss. Inaug. Dorpati Livonorum, 1851. This tract, which had been almost forgotten by physiologists, has been reprinted in substance by J. Steiner, in *Archiv f. Anat. Phys. u.s.w.* 1873, p. 137.

laboratory in the Harvard Medical School. He finds that oils pass more readily through membrane or plaster wet with bile than through membrane or plaster wet with water. This is increased if the bile be alkaline and decreased if it be acid.

He concludes that the action cannot be due to the bile changing the form of the pores; and he finds also that after passing through membranes moistened with bile, the fats appear more finely divided than when passed through membranes wet with other fluids; and he infers that the drop-tension or cohesion of the fat has been affected.*

Thirty years ago it was denied that bile had the property of turning starch into sugar; but von Wittich has shown that this office is enjoyed by fresh human bile as well as that of many animals.† Bufalini has of late confirmed this observation of von Wittich's, and further finds that fresh bile has also the property of changing the hepatic glycogen into sugar. When bile is deprived of its mucus and pigments by means of slight acidulation with acetic acid and animal charcoal, it still retains this power; but the change is longer in being accomplished, probably because some of the ferment is carried away with the mucus. Putrefying bile does not change starch or glycogen into sugar; nor do the bile acid salts.‡

Upon the sugars themselves bile appears to have no more action than other animal matters have. Thus it forms lactic acid if kept for a long time with

* Charles H. Williams, *Experiments on the action of Bile in promoting the absorption of Fats*, Prize Essay of the Boylston Medical Society for 1874, published as Supplement to the ninetieth volume of the *Boston Medical and Surgical Journal*.

† von Wittich, *Arch. f. d. ges. Phys.* 1872, Bd. vj. p. 182. H. Hoffman (Häser's *Archiv* 1844, Bd. vj. p. 157, Bericht in *Arch. f. Anat. Phys. u.s.w.* 1846, p. 27) distinctly says that bile can turn starch (Kleister) into dextrin and sugar.

‡ Bufalini, *Lo Sperimentale*, abstract in *London Medical Record*, 1879, p. 149.

grape sugar or cane sugar.* It was once thought that bile could turn sugar into fat;† a notion refuted by the experiments of Schiel,‡ and Frerichs.§

Bile has no solvent action on the albumens. Hünefeld noticed that the bile dissolved the red blood corpuscles|| and this property was extended to the more important articles of diet, so that Platner allowed a certain small power in bile to dissolve loosely-clotted albumen, fibrin, and casein.¶ The experiments of von Gorup-Besanez** showed that bile had no influence on white of egg, boiled or fresh beef, but seemed to favour the idea that cheese was dissolved by bile. This has been disproved by the experiments of Bidder and Schmidt.††

A strange view of the office of the bile was entertained by Prout. "If the food originally contained no albuminous matter; no albumen is developed in the stomach; but immediately on the entrance of the semi-fluid mass into the duodenum, and its mixture with the bile and the pancreatic fluids; albuminous and other chylous matters, become distinctly perceptible." Later on he says that some of the albumen may be developed from the pancreatic fluid, but the whole is too great to be explained in this manner.‡‡

It was known early in this century that the chyme

* Bence Jones, *Medical Times*, 1851, July 5, p. 3. This is probably copied from Frerichs, who says the same thing. (Wagner's *Handwörterbuch d. Physiologie*, Branschweig, 1846, Bd. iii. Abth. i. p. 835.)

† Henr. Meckel ab Hemsbach *de genesi adipis in animalibus* Diss. inaug. med. Halis; quoted in Canstatt's *Jahresb. f.* 1845, Bd. i. p. 145.

‡ Schiel, *Zeitschrift f. rat. Med.* 1846, Bd. iv. p. 375.

§ Frerichs, *loc. cit.*

|| Hünefeld, *Der Chemismus in der thierischen Organisation*, Leipzig, 1840, p. 102.

¶ Platner, *Ueber die Natur u.d. Nutzen d. Galle*, Heidelberg, 1845, p. 124.

** E. von Gorup-Besanez, *Untersuchungen ueber Galle*, Erlangen, 1846, p. 46.

†† Bidder and Schmidt, *op. cit.* p. 219.

‡‡ Prout, *Chemistry, Meteorology, and the Function of Digestion considered with reference to natural Theology*, Bridgewater Treatise, London, 1834, p. 508.

was thrown down when brought into contact with bile.* It was also demonstrated by Eberle† and insisted on by nearly every physiologist after him. Platner apparently believed that the precipitate was a combination of the bile acids with albumen or pepsin.‡ He stated that the combination of bile acids and albumen could hardly be digested even if kept for days with artificial gastric juice.

It was very distinctly taught by Claude Bernard that if bile be added to the gastric juice, the work of digestion is at once arrested. If meat be kept in gastric juice at the proper temperature, the particles of the muscular fibres are broken up, and this is the peculiar office of the gastric juice. But if bile be added, the process ceases at once. The presence of bile in the stomach puts an end to digestion. Even if the gastric juice remain acid, it loses its digestive properties.

When the albuminous bodies which have been dissolved by the gastric juice arrive in the duodenum, they are at once thrown down by the bile; but the bodies free from nitrogen remain untouched. No precipitate is formed if bile be added to the gastric juice from a fasting animal, or from one which has eaten only fat, starch, or sugar. But when the nitrogenous elements of the food pass through the pylorus, a yellow precipitate is thrown down of everything dissolved, and this precipitate adheres to the walls of the gut. The viscid secretion of the duodenal glands helps to entangle the precipitate, and to keep it in the duodenum, to undergo for a longer time the action of the digestive fluids.

By the precipitation of the chyme by the bile, the activity of the gastric juice is wholly brought to an

* Autenrieth, *Handbuch d. emp. mensch. Physiologie*, Tüb. 1802. Bd. ij. p. 98. Werner, quoted by Eberle, *Physiologie der Verdauung*, Würzburg, 1834. p. 210. Blundell, 1817, quoted by Elliotson, *Human Physiology*, London, 1840. p. 101, note.

† Eberle, *Physiologie d. Verdauung*, Würzburg, 1834, p. 190.

‡ Platner, *Ueber die Natur und den Nutzen der Galle*, Heidelberg, 1845, p. 126.

end. If the chyme be filtered, the filtrate has no longer any digestive power.*

That the gastric juice holding peptones in solution is thrown down, and rendered inactive, by the addition of bile, is assented to by nearly every physiologist. Dr. Dalton, however, says that he has invariably found that if the gastric juice be digested with white of egg, the filtered fluid will no longer give the slightest precipitate on the addition of bile.†

According to Claude Bernard, the precipitate thrown down by the bile from the chyme is redissolved by the pancreatic juice. Also if pieces of the food, such as casein or flesh, not yet entirely dissolved by the gastric juice, be acted on by bile, digestion begins anew as soon as the pancreatic juice is added. This renewal of digestion does not take place unless the chyme have first been subjected to the interruption of digestion by the bile; so the interruption by the bile seems needful to render the pancreatic juice active, and the order of succession would be (i.) gastric juice (ii.) bile (iii.) pancreatic juice.‡ This is somewhat in opposition to the experience of physiologists who find that digestion goes on much the same in the intestines after tying the common duct; and especially to those experiments of Bidder and Schmidt who found all the elements of the food well digested, save only the fats and oils.§

Tiedemann and Gmelin,|| Frerichs,¶ and an observer so late as Lucien Corvisart,** taught that it was not the

* Claude Bernard, *Leçons de Physiologie exp.* Paris, 1856, t. ij. p. 421.

† John C. Dalton, *A Treatise on Human Physiology*, Philadelphia, 1871, Fifth ed. p. 180.

‡ Claude Bernard, *op. cit.* t. ij. p. 441. See the observations of Heidenhain on the pancreatic juice and bile below. (p. 143.)

§ See above, p. 136.

|| Tiedemann and Gmelin, *Recherches expérimentales, etc. sur la digestion*, Jourdan's transl. Paris, 1827, Partie ii. p. 395.

¶ Frerichs, Wagner's *Handw. d. Phys.* Braunschweig, 1846, Bd. iii. Abth. i. p. 834.

** Lucien Corvisart, *Comptes rendus*, 1857, t. xlv. p. 720.

albuminous parts of the chyme that were thrown down by contact with the bile, but the mucus and colouring matters of the bile itself. Brücke has tried to disprove this by removing the mucus of the bile by rendering the bile acid with phosphoric acid, filtering, and then adding the filtrate to chyme; there is thrown down an abundant white precipitate, composed of peptones.* Schiff criticises this, for he says that although Brücke's statements are true, yet his interpretation is false. They prove nothing about the physiological action of the bile upon the chyme. Schiff finds that it is only when the bile is rendered more acid than the gastric juice, that a precipitate of peptones is thrown down. He does not, however, deny that bile throws down peptones. Indeed, he recommends this humour as a substitute for Millon's reagent in ascertaining the presence of albuminates not thrown down by heat.†

According to Burkart the bile has a very distinct action upon the gastric juice. A precipitate is thrown down which on examination is found to be a mixture of the pepsin of the gastric juice with the bile acid, and the supernatant fluid is devoid of any digestive power.‡ This precipitation Burkart thinks is due to the presence of glycocholic acid in the bile, not to taurocholic acid.§ The acid of the gastric juice separates the glycocholic acid from its base and this acid is thrown down with the pepsin mechanically adhering.

Hammarsten finds that the digestive power of the gastric juice is destroyed by the bile of many species of mammals, and also of birds and fishes. He thinks it may be a common property of the bile of all vertebrate animals.

* Brücke, Moleschott's *Untersuchungen zur Naturlehre*, Giessen, 1862, Bd. viii. p. 335.

† M. Schiff, *Arch. f. d. ges. Phys.* 1870, Bd. iii. p. 620.

‡ Burkart, *ibid.* 1868, Bd. i. p. 208.

§ Idem, *ibid.* 1869, Bd. ii. p. 182.

He further finds that a precipitate is not always formed by the addition of bile to the gastric juice,* but only when the gastric juice contains albumen; and that the digestive power of the gastric juice may be taken away even while the fluid remains quite clear. The pepsin, however, is not decomposed by the bile acids, for it can be found again. Cubes of hard-boiled white of egg or shreds of fibrin are not acted on at all by gastric juice, if they be kept beforehand for a few hours in a mixture of gastric juice and bile, or of hydrochloric acid and bile. This is due to some union between the bile and the albumen; for he found in the experiments just mentioned that the amount of solids in the gastric juice always decreased, while the weight of the cubes of hard-boiled white of egg increased. Apparently there is a chemical union between the bile acids and the albumen.

He finds also that glycocholic acid is less active than bile itself, and that taurocholic acid is more active than glycocholic acid in destroying the digestive properties of the gastric juice. In this matter he is in direct contradiction with Burkart. He thinks it possible also that the other elements of the bile may have some share in destroying the power of pepsin; but as no means are known of dissolving cholestearin or the pigments but by agents which would at the same time greatly disturb digestion, the question at present cannot be settled.†

In contrast to the action of bile upon gastric juice, Heidenhain found that when bile is added to pancreatic juice in action, the process is not put a stop to, but is rather favoured.‡

According to Hoppe-Seyler's observations, the pan-

* This exactly agrees with the statement of Claude Bernard, who found that no precipitate followed the addition of bile to the gastric juice from an animal fasting. (*Leçons de Physiologie exp.* Paris, 1856, t. ii. p. 422.)

† O. Hammarsten, *Arch. f. d. ges. Phys.* 1870, Bd. iii. p. 53.

‡ Heidenhain, *ibid.* 1875, Bd. x. p. 579.

creatic juice does not seem to split up the bile acids into cholalic acid, taurin, and glycocoll, with any very great rapidity.*

I have not met with any direct experiments as to the action of the bile upon the *succus entericus*, but the bile is also said to stimulate the secretion of the intestinal juice, and to increase the peristaltic movements.† In favour of this, Tiedemann and Gmelin found that the fæces of animals whose bile ducts had been tied were very firm, and that the dogs were constive.‡ The same thing has been noted in dogs in whom a biliary fistula has been set up.§

Eberle found that the bile acted on the bowels as an irritant, increasing their movements, and causing an abundant secretion from the mucous membrane;|| and Schülein has lately said that the administration of the bile acids, whether by the mouth or by the veins, is followed by purging and vomiting; and that cholalic acid is more active in this way than glycocholic or tau-rocholic acid. He thus thinks it likely that the bile may increase the peristaltic movements of the intestines,¶ as Eberle has suggested.

Another use of the bile was formerly thought to be the neutralisation of the acid of the gastric juice;** but

* Hoppe-Seyler, *Arch. f. path. Anat.* 1863, Bd. xxvi. p. 532.

† Saunders thought this to be its principal office. (*A Treatise on the Structure, Economy, and Diseases of the Liver*, Lond. 1803, Third ed. p. 151.) and Sir Thomas Browne (*Pseudodoxia Epidemica* or *Enquiries into Vulgar and Common Errors*, Book iii. Chapter ii. London, 1650. Sec. Ed. page 88.) expresses the common belief of the 17th and 18th centuries when he says: Cholera is the naturall glisten, or one excretion whereby nature excludeth another; which descending daily into the bowels, extimulates those parts, and excites them unto expulsion. And therefore when this humour aboundeth or corrupteth, there succeeds oft times a *choleric passion*; that is, a sudden and vehement purgation upward and downward.

‡ Tiedemann and Gmelin, *op. cit.* Partie ii. pp. 47 and 70.

§ Schwann, Bidder and Schmidt, *ll. cit.*

|| Eberle, *Physiologie der Verdauung*, Würzburg, 1834, p. 314.

¶ M. Schülein, *Zeitschrift f. Biologie*, 1877, Bd. xiii. p. 172.

** Boerhaave is said by Tiedemann and Gmelin to have been a supporter of this theory. (Tiedemann and Gmelin, *op. cit.* Partie i. p. 384.) I can hardly think

as the bile is commonly neutral in reaction, and but rarely alkaline, it is clear that this cannot be its chief office. This view prevailed longer than natural; for it was adopted by C. H. Schultz in his theories on the amount of the bile, and these again were brought into prominence by Liebig.*

The bile is thought to hinder putrefaction. Bidder and Schmidt,† with other observers, noted the disgusting smell of the fæces and flatus of dogs in whom the bile had been diverted from the intestines. The same thing is said to be seen in jaundice, though I can hardly assent myself to this as a general rule. The bad smell is attributed to the lack of the antiseptic action of the bile. Saunders attributed the antiseptic powers of bile to its bitterness, and found by experiment that bile became putrid less readily than blood.‡ Von Gorup Besanez thinks the antiseptic powers of the bile due to the bile acids. He put meat and albumen into a solution of the bile acids, and kept the mixture for 48 hours at the temperature of the body. At the end of this time there was no trace of putrefaction; while meat and albumen put into plain water and treated in the same way gave distinct signs of putrefaction at the

that Boerhaave was of opinion that the bile had an alkaline reaction. Speaking of the properties of the cystic bile, he says: "nec alcalica est, nec acida." (*Opera Omnia Medica*, Venetiis, 1757, p. 20. *Institutiones Medicæ*, § 99.) On the other hand he says a little later on: (p. 22 § 107) "Bilis Alcalina acidum Chylum fixum in salsum volatile Alcalescens immutans; Pancreaticæ Lymphæ acor et cum bile Alcalina fervor; . . . et innumeræ tales hypotheses, damnosæ, dum, regulas dant faciundæ Medicinæ."

Kemp (*Lond. Med. Gaz.* 1845, vol. i. p. 77.) says he has examined 200 samples of bile and found them all neutral.

* See p. 94 of this work.

† Bidder and Schmidt, *op. cit.* p. 104.

H. Hoffmann is said to have an important paper on the antiseptic powers of the bile, (*Häser's Archiv* 1844, Bd. vi. p. 157.) but I have not been able to see a copy of this in London.

‡ Saunders, *op. cit.* pp. 136 and 155.

end of 24 hours.* He found also that fermentation set in much later when bile was mixed with syrup, urine, and the like, than without. This experiment has been confirmed by Claude Bernard, who found that bile at once checked the fermentation of yeast from the stomach of a dog.†

More lately Stolnikoff has made a few experiments in Hoppe-Seyler's laboratory at Strassburg on this point: Bile and water; fibrin, bile, and water; fibrin, fat, and water; and fibrin, fat, bile, and water were left in bottles from the middle of June to the middle of August, and the gases given out collected over mercury. The bile simply mixed with water had given out no gas; but the mixture of fibrin and fat without bile had given out most of all. The gas showed 92 *per cent.* of carbonic acid. The contents of the bottles showed the bile acids split up into cholalic acid, taurin, and glycocoll, as might have been looked for. Stolnikoff concludes that bile is able for a short time to delay putrefaction, but not to hinder it altogether, as the bile and water itself had split up into new products, although no gas had been given off. Stolnikoff does not think that the office of the bile is to stop putrefaction in the intestines, but rather to favour absorption.‡

Haller thought that the use of the bile was to aid in the solution of the food, and to form one homogeneous mass with mucus, oil, and water, by trituration and the peristaltic action of the bowels.§

Changes of the bile in the intestines.—After the bile has been poured into the duodenum, and done what-

* E. von Gorup-Besanez, *Untersuchungen ueber Galle*, Erlangen, 1846, pp. 48 and 50. The first of these experiments was made with the same result by Platner. (*Ueber die Natur und den Nutzen der Galle*, Heidelberg, 1845, p. 128.)

† Claude Bernard, reported by Donaldson, *American Journal of the Medical Sciences*, 1851. Vol. xxii. p. 351.

‡ J. Stolnikoff, *Zeitschrift f. phys. Chemie*, 1878, Bd. i. p. 343.

§ Haller, *Elem. Phys.* Lugd. Bat. 1764, t. vi. p. 608.

ever it is appointed to do, whether it be a positive harm to the process of digestion, a suggestion which in the present state of knowledge may perhaps be entertained; or be simply an indifferent fluid; or in some way aid the pancreatic juice; what becomes of the humour? Does it pass entirely out of the body with the fæces, or is it absorbed again into the circulation?

Liebig and his followers assumed that the greater part of the bile was absorbed to aid in the combustion of respiration.* Mulder, on the other hand, taught that the greater part of the bile was passed out by the anus,† while Frerichs held that neither of these views was wholly correct,‡ at the same time stating that of the bile only a small part was absorbed.

Bidder and Schmidt, in order to settle this question, estimated the amount of bile in the fæces passed in five days by a dog weighing 8 kilogrammes. The fæces weighed 97·3 gm. of which 40·9 grammes were solid. Now the solids of the bile passed in five days would be 39·52 gm. that is nearly equal to the solids of the fæces; yet the fæces showed but small traces of the presence of bile. Still more important was the amount of sulphur in the fæces. The bile of dogs holds about 6 *per cent.* of sulphur: so that in 39·52 gm. of solid bile, there should be nearly 2·37 gm. of sulphur. As a fact, the fæces only held 0·334 gm. of sulphur; and without doubt more than half of this came from the numerous hairs in which the fæces abounded.§

It was said by Frerichs in 1846 that as soon as the

* Liebig, *Animal Chemistry*, London, 1842, Gregory's translation, Sec. Ed. pp. 60-66.

† Mulder, *Untersuchungen über die Galle*, Frankf. a. M. 1847, p. 107. He teaches that the bile begins to decompose as soon as it is secreted.

‡ Frerichs, in Wagner's *Handwörterbuch d. Physiologie*, Braunschweig, 1846, Bd. iii. Abth. i. p. 839.

§ Bidder and Schmidt, *op. cit.* p. 217.

bile entered the intestine, the bile acids broke up into taurin, chloidic acid, and dyslysin, and that in the end only dyslysin could be detected. The pigment is described as passing from green into brown, and at last attaining the characters of the colouring matter of some gall stones.* The cholestearin at this time seems to have been neglected.

But in 1862 Hoppe discovered the presence of free cholalic acid in the fæces of dogs,† and in a few months the same observer announced that, as well as cholalic acid in quantity, he found undecomposed glycocholic and taurocholic acid in the fæces of dogs and cows, and certain elements of the bile in the fæces of pigeons, and in guano from Peru. He estimated the amount of cholalic acid in the fæces of a dog weighing 8 kilogrammes and fed on beef. The weight of the fæces for three days was 287 grammes, and the amount of cholalic acid was 1.1 gm. estimated by the polariscope. This equals .36 gm of cholalic acid a day, or .45 gm. of taurocholic acid. Now taking Bidder and Schmidt's estimate for the amount of solids in the bile excreted by a dog of this weight as 8 gm. in 24 hours,‡ and one half of this as made up of bile acids, there will be at the most only half a gramme out of 4 grammes of bile acids accounted for in the fæces. What becomes then of the remaining three and a half grammes?

Hoppe-Seyler analysed the contents of different parts of the intestines of dogs and rabbits, and found that though the splitting up of the taurocholic acid began in the small intestine, yet it chiefly progressed in the large intestine. He thinks it a spontaneous change; for none of the secretions poured into the intestine con-

* Frerichs, in Wagner's *Handwörterbuch d. Physiologie*, Braunschweig, 1846. Bd. iii. Abth. i. pp. 840 and 841.

† Hoppe, *Archiv. f. path. Anat.* 1862, Bd. xxv. p. 181.

‡ See p. 100 of this work.

tains a ferment capable of setting the change in motion: also that the change is quite analogous to that of the splitting up of hippuric acid, and notes that the fæces of dogs hold a quantity of free butyric acid, valerianic acid, caproic and caprylic acid, products of decomposition in the large intestine.*

It will have been seen above that Hoppe-Seyler and his followers assert that the bile acids become decomposed in the intestines into taurin and glycocoll, with the formation of free cholalic acid. Uncombined taurin and glycocoll are not found in the fæces, so it is probable that they, or the products of their decomposition, are absorbed again into the blood. Schultzen and Nencki, in their admirable research into the decompositions which lead to urea, found that when an animal, the amount of urea in whose urine was constant, was fed with glycocoll, the urea was at once increased to an amount equivalent to the amount of glycocoll ingested. Glycocoll, therefore, on its way through the œconomy becomes changed into urea, and in this way leaves the body.† Taurin would also seem to pass out of the body by the urine, as Salkowski found that in man taurin given by the mouth again appeared in the urine, partly as unchanged taurin, but in great part as an acid containing sulphur and nitrogen (tauro-carbamic acid) the normal sulphates not being increased.‡

If some of Ernst Bischoff's estimations were accepted as representing a general rule, there might be no need of discussing further the fate of the bile in the intestines. He found the fæces rich in bile, about 10 *per cent.* of unaltered bile acids, while the cholalic and choloidic

* Hoppe-Seyler, *ibid.* 1863, Bd. xxvi. p. 519.

† Schultzen and Nencki, *Zeitschrift f. Biologie*, 1872, Bd. viii. p. 132.

‡ Salkowski, *Berichte der deutschen chem. Gesellschaft zu Berlin*, 1872, Jahrg. v. p. 637. See also an abstract by himself in Virchow and Hirsch's *Jahresbericht f.* 1873, Bd. i. p. 159.

acids were not more than 1 *per cent.* Altogether he thinks that man passes daily *per anum* about 5 grammes of solid bile.* Now 5 grammes of solid bile would be about the amount secreted daily by the liver in the cases of biliary fistula in man observed by Dr. Robinson and Krumptmann,† and Leyden adopts 2 to 4 grammes as the amount of bile acids daily secreted by the liver.‡ Calculations of this sort must not be pressed too far, as there appear to be as great variations in the amount of bile secreted by man as by any other animal.

In 1869, Schiff announced that the bile acids and bile pigments are again absorbed into the portal circulation and again excreted by the liver. In a dog, upon whom a biliary fistula had been made, the amount of bile excreted was about 2 C.C. in 20 minutes. If 180 C.C. of fresh ox bile were now injected into the duodenum, a surprising increase of the amount of bile took place; so that in a very short time 10 C.C. of bile could be collected in 20 minutes from the fistula, and at the end of an hour 8.5 C.C. in 20 minutes. Schiff then availed himself of a statement of Heidenhain's, that the bile of the guinea-pig gives no reaction with Pettenkofer's test. He established a fistula on a guinea-pig, and found no decided reaction in the bile when tested by Pettenkofer's test; ox bile was then injected into the duodenum, and in half an hour, and up to 1, 2, or 3 hours after, the bile gave a marked reaction with Pettenkofer's test, just as if ox bile had been diluted with 2 or 3 times its volume of water. As to the pigments, the natural colour of the bile of dogs is a golden yellow; when ox bile was introduced into the duodenum of dogs, the bile became dark and brown.

* Ernst Bischoff, *Zeitschrift f. rat. Med.* 1864, Bd. xxi. p. 143.

† See p. 97 of this work.

‡ Leyden, *Beiträge zur Pathologie des Icterus*, Berlin, 1866, p. 55.

The phænomena prove in Schiff's opinion that there is a circulation of the bile, as well as of the blood; that the bile is poured out by the liver into the intestine, there again to be taken up by the mesenteric vessels, carried to the liver, and again excreted into the duodenum.* In another article, he repeats his belief that the secretion of bile is almost wholly dependent on absorption from the intestine, and that if the bile be cut off from the intestine, little or no bile is secreted.†

Theodor Laffter, under Heidenhain's direction, has repeated Schiff's experiments, and differs from him considerably in his results. When ox bile was injected into the duodenum of guinea pigs, a very slight increase of the amount of bile was seen in some, in others a decrease. Laffter does not attribute this decrease to the action of the bile, but to a peculiarity of the animal. Laffter agrees with Schiff in announcing an increase in the solid bile, but the amount seems to me so small that it may easily be within the boundaries of physiological variation. In one matter Laffter has made a curious observation; he finds that colouring matters, such as rhubarb and indigo-sulphate of soda, injected into the duodenum, very rapidly appear in the bile; in one reading of the text, Laffter may be thought to say within a minute after the injection into the duodenum.‡

Following upon Laffter, Prince Tarchanoff entered upon a research to show that the liver has also the power of rapidly excreting other colouring matters. If blood colouring matter or bilirubin be injected into the veins of a dog with a biliary fistula, a great increase of the water and pigments of the bile follows.§

* M. Schiff, *Giorn. di Scienze Naturali ed Econ.* Palermo, 1869, vol. iv. p. 9.

† M. Schiff, *Arch. f. d. ges. Phys.* 1870, Bd. iii. p. 598.

‡ Theodor Laffter, *Versuche zur Physiologie der Gallensecretion*, Diss. Inaug. Breslau, 1873. It is not so clearly expressed as I could wish that this last colouring matter was injected into the duodenum. I am indebted to Dr. Lauder Brunton for the opportunity of seeing the original dissertation.

§ Johannes, Fürst Tarchanoff, *Arch. f. d. ges. Phys.* 1874, Bd. ix. p. 329.

Huppert's observations are generally quoted as if they gave aid to Schiff's belief that the bile acids are excreted by the liver. He injected a certain quantity of bile acids into the circulation of a rabbit in whom a biliary fistula had been set up, and found that the liver excreted about the fourth to the third part of the bile acids injected.*

Socoloff has repeated, in Hoppe-Seyler's laboratory, some experiments like those of Schiff, but he has not obtained precisely the same results. After the injection of the glycocholate of soda into the veins or stomach of dogs, he found indeed that there was an increase, very marked, of the amount of bile secreted. And this increase took place, as Schiff found it, within 15 minutes after the injection. With this increase of the bile itself, there was always a marked decrease of the amount of bile acid salts. There was not the least increase of the solids of the bile. Now if this be maintained, a blow will certainly be dealt to the views of Schiff and his followers, as Schiff himself expressly states that there is an increase in the amount of the solids of the bile.†

Socoloff notes also that in Huppert's experiments the increase of bile after the injection of bile acids was first noted in the second hour, just as Bidder and Schmidt did in their experiments without injection. He criticises justly also Schiff's observations on guinea pigs, noting that Pettenkofer's test is not enough alone to enable a man to assert the presence of bile acids, but that the bile acids should be crystallised out, as Socoloff has done.‡

It may be noted also that Laffter§ and Külz|| deny

* Huppert, *Archiv der Heilkunde*, 1864, p. 244.

† Schiff, *Arch. f. d. ges. Phys.* 1870, Bd. iii. p. 599.

‡ Socoloff, *ibid.* 1875, Bd. xi. p. 166.

§ Laffter, *op. cit.* p. 11. Work done in Heidenhain's laboratory.

|| Külz, Virchow and Hirsch's *Jahresbericht f.* 1875, Bd. i. p. 219.

the statement of Schiff that the bile of guinea pigs gives no reaction with Pettenkofer's test. And it must be owned that it does seem highly improbable that the bile of a vertebrate should be without evidence of the presence of bile acids.

Tappeiner has also made estimations on the absorption of bile acids by the small intestine. Dogs were fasted for 24 hours, and then a certain quantity of dog's bile, or a solution of glycocholate of soda, injected into a tied-off part of the small intestine. After the bile acid salt or the gall had been left in the bowel from 3 to 5 hours, the amount of bile acids and of sulphur was estimated. In the upper part of the small intestine, the duodenum and jejunum, the whole of the sulphur of the bile was found again; in the ileum, never more than one third. Of glycocholate of soda none was absorbed in the duodenum; but in the jejunum and ileum, never more than one half could again be found.

Tappeiner refuses to admit a chemical change as the cause of a decrease in the amount of bile acids found. The first step in a chemical change would be the decomposition of the bile acids into cholalic acid, taurin, and glycocoll. Now it was found that taurin is readily absorbed by the intestines of dogs; but when taurocholic acid was injected into the jejunum, the whole quantity injected was found again.* It may be admitted that there is no decomposition in the parts of the intestines where the amount of bile acids injected was again recovered, but this will hardly be allowed to hold good for the ileum, where only one half or one third of the bile acids could again be recovered, and which may therefore have undergone the decomposition in question before they were absorbed.

Amongst the older authors, Tiedemann and Gmelin

* Tappeiner, in von Buhl's *Mitt. aus d. path. Inst. zu München*, Stuttgart, 1878, p. 218.

found cholestearin in the contents of the small intestine of certain mammals, and in the large intestine of the calf.* But Dr. Austin Flint, the younger, is of opinion that no cholestearin can be found in normal fæces, only a product of the decomposition of cholestearin, named serolin by Boudet, but which Dr. Flint calls stercorin.† The elimination of cholestearin he looks upon as a most important office of the liver. Hoppe-Seyler, commenting upon the observations of Dr. Austin Flint, says that he has always found cholestearin in the fæces of dogs, oxen and men; and he does not doubt that Dr. Flint's stercorin and Boudet's serolin are but impure cholestearin.‡ Dr. Flint's theory would in this case fall to the ground, if Hoppe-Seyler's facts be accepted; and I think that evidence offered by this distinguished chemist on a matter like the finding of cholestearin will be hard to be overturned.

Beneke also looks upon the excretion of cholestearin by the liver as a function most important to the œconomy; but he does not, like Dr. Flint, think cholestearin a mere excremental product. Rather noting the wide-spread distribution of this body in both the animal and vegetable kingdom, being found in the seed of both plants and beasts, in the milk, in the chyle, the serum and corpuscles of the blood, in the marrow of bones, and above all in the nervous system, he thinks it must serve other uses than that of a mere excrement. The liver is, according to Beneke, the organ in which cholestearin, and its attendant, lecithin, are formed; with the bile they pass into the intestine, and thence all over the body. In Beneke's view, therefore, cholestearin and lecithin would be two

* Tiedemann and Gmelin, *op. cit.* partie i. pp. 395 and 404.

† Austin Flint, *Recherches exp. sur une nouvelle fonction du foie*, Paris, 1868. *passim*.

‡ Hoppe-Seyler, in Virchow and Hirsch's *Jahresbericht f.* 1868, Bd. i. p. 97. See also *Arch. f. path. Anat.* 1863, Bd. xxvi. pp. 527, *et seq.*

of the most important physiological compounds and certainly the most important of those found in the bile.*

To what purpose, then, serves the bile? It cannot be looked upon solely as an excrement, for it has been seen what deep changes in nutrition follow its diversion from the body. There is no evidence that it is necessary for the completion of the process of digestion in the stomach or intestines; indeed it may be said by some physiologists that it does harm to the process in either viscus. The view that it acts as a sort of natural purge has little against it; but, at the same time, there is but little in its favour. As to the power of the bile in arresting putrefaction, it would seem that it must be small, if, as soon as it arrives in the intestine, it begin itself to undergo putrefactive changes. The view that the bile neutralises the acid of the chyme must fall with the establishment of the fact that the bile is not alkaline but neutral in reaction. The only office which remains to it is that of emulsifying fats, a property known to the Greeks 2200 years ago, and of changing starch into sugar. It is melancholy to find that in so many years nothing more is known with certainty as to the uses of this long-studied humour.

It has seemed to me that physiologists are drifting into the belief that the office of the bile is not to act upon the chyme or to assist in the first digestion of aliments. Rather its office is to pass into the intestine, there to undergo changes itself, the products of decomposition being absorbed into the blood, and leaving the body by the urine. If it be admitted that the bile acids be decomposed before they be absorbed, it is most probable that they split up into glycocoll, taurin, and cholalic acid. The glycocoll, it has been seen above, is one of the bodies which, when taken into the intestine, appears

* Beneke, *Grundlinien der Pathologie des Stoffwechsels*, Berlin, 1874, p. 194.

in the urine as urea ; taurin, in like manner, appears in the urine, probably furnishing the unoxysed sulphur of this secretion, though, according to Salkowski* it can no longer be thought that in man it is the source of the oxydised bodies, the sulphates. In rabbits, the ingestion of taurin is still followed by a great excess of sulphates in the urine. The cholalic acid would appear to leave the body by the fæces ; but a theory might be made by adopting Schiff's view of a circulation of the bile ; supposing a salt of cholalic acid to be absorbed and conveyed to the liver, and there to unite with freshly made taurin and glycocoll, and again to be excreted by the bile. Of the destiny of the bile pigments, little has been yet said ; by some it is thought that they undergo oxydation† in the intestines ; by others, reduction ;‡ but the product of the change, whatever it may be, is called, by Vanlair and Masius, stercobilin ;§ a pigment which is closely allied to that colouring matter of the urine named urobilin by Jaffe.|| It thus becomes possible that the bile pigments, after suffering whatever chemical change they may be destined to undergo in the bowel, are absorbed into the blood and excreted by the urine as colouring matter, while the remainder passes out with the fæces. The end of the bile would thus seem to be excretion by the urine ; a view not altogether new, for it was taught by physiologists sixteen hundred years ago that the urine was formed in the liver, and separated by the kidneys ; and those who come after us may judge whether the nineteenth century have made any real progress in this matter compared with the age of Galen.

* Salkowski, Virchow and Hirsch's *Jahresbericht f.* 1873, Bd. i. p. 159.

† Heynsius and Campbell, *Arch. f. d. ges. Phys.* 1871, Bd. iv. p. 497.

‡ Maly, *Annalen d. Chemie u. Pharm.* 1872, Bd. clxiii. p. 77.

§ Vanlair and Masius, *Centralblatt f. d. med. Wiss.* 1871, p. 369.

|| Jaffe, *Arch. f. path. Anat.* 1869, Bd. xlvii. p. 423.

CHAPTER VIII.

ACTION OF DRUGS UPON THE SECRETION OF THE BILE.

THE notion of a drug which should have a special action on the bile is as old as Hippocrates,* although the word cholagogue does not appear to have been much used before the time of Galen. Certain drugs were commonly supposed in former times to increase the amount of the bile secreted by the liver, because the patient passed stools of yellow or dark colour after the drug had been administered. It is clear that no reasoning can be more fallacious. The colour of the stools depends not so much on the amount of bile secreted, as on the length of time that the fæces have sojourned in the intestines, or on the diet of the patient. If they should be hurried through the intestines, they may even contain unaltered bile; if the patient have taken abundance of milk, they will be almost colourless. It is plain that no trustworthy information can be had, save from the observation of the amount of bile discharged by a biliary fistula. In man, it has already been said, biliary fistulæ are rare, and in this way knowledge has been but little increased.

In Westphalen's case, indeed, a dose of calomel (1·3 gramme = 20 grains) was once given to the patient, but without causing any increase, rather a decrease, of the amount of bile.† Quinine, given in doses of 2 grammes, (30 grains) could not be found in the bile.

Observations on animals with artificial biliary fistula are, then, the only means by which information is to be had; and Hermann Nasse, the first to make observa-

* Hippocrates, *De nat. hom.* Cap. 5, Littré's ed. t. vi. p. 42.

† Westphalen, *Deutsches Arch. f. klin. Med.* 1873, Bd. xi. pp. 598 and 600.

tions on the amount of bile secreted by the dog, was also the first to test the effect of drugs on the bile. He reports that calomel increased the amount of fluid bile but decreased the solids, and that large doses of carbonate of soda decreased both the fluid and solid bile.* As the preparations of mercury are those which have enjoyed the greatest reputation for increasing the secretion of bile, it will be found convenient to discuss them first before the action of other drugs be considered, especially as observers differ, more or less, in their results.

Nasse, it has been said, appears to have been the first to note the effect of calomel in a dog in whom a biliary fistula had been set up. The observations were made in the month of November, the dog being kept upon the same food throughout, apparently bread and potatoes, and from the 6th to the 15th of the month, carbonate of soda having been added to the food. From Nov. 24 to 27, a gramme of calomel was given within 36 hours with the food. The first day, the dog left half the food set before it; the second, at mid-day, it showed no appetite; but on the third day it left nothing. The amount of bile was less on the first day, but much increased on the two following. The first night, after that the dog had taken .75 grm. of calomel, the amount of bile secreted, 36.8 grammes, was of a high specific gravity (1.015.7).† The mean of the two last days was 212.55 fluid bile, and 4.388 grm. of solid bile. The mean of eight days before the mercury was 126.5 grm. of fluid bile, and 2.887 of solid bile; so that the amount both of fluid and solid bile would seem to be increased.

* Nasse, *Commentatio de bilis quotidie a cane secreta copia et indole*, Marburg, 1851, p. 18 *et seq.* Those who wish to see the history of opinions on mercury as a cholagogue may consult Dr. Fraser's article in the *Edinburgh Medical Journal*, April, 1871, vol. xvi. p. 904.

† Nasse, *op. cit.* p. 11.

Kölliker and Müller gave four grains of calomel to one of their dogs, at 10 a.m. on the 26th day after the biliary fistula had been set up. Five observations in the afternoon gave as a mean for every half hour 3·823 gr. which was not much over the ordinary average. The next day, four observations gave 3·267 gr. as mean, which was therefore somewhat less than customary. On the 21st and 29th days, the dog was again given four grains of calomel; but the mean of seven observations gave only 2·183 for every half hour. The bile also became brownish and thick so that it would hardly flow. But it should be noted that the dog's health was bad; it was losing weight, and had diarrhœa; the stools were not green but grey; later on they were bloody. For some days the dog would only take bread and milk.*

Dr. George Scott, in 1858, in Dr. Lionel Beale's laboratory, set up a biliary fistula in a dog; he calculated the amount of fluid bile and solid bile secreted in 24 hours, for two days, before calomel was given; and also the average amount secreted in 24 hours, for two days, after the calomel was given. He thought that the action of the calomel would last longer than 24 hours. The bile was collected twice a day, morning and evening. The calomel was given each time after the morning's bile was collected, and therefore the effect of medicine would be upon the bile of the day following. There were four trials of the calomel; and all four gave, in Dr. Scott's opinion, but one result, "a diminution in the amount of fluid bile and bile-solids secreted after the administration of large doses of calomel."†

The details of the experiments made by Dr. Scott are

* Kölliker and Müller, *Verhandlungen der phys.-med. Gesellschaft in Würzburg*, 1855. Bd. v. p. 231.

† George Scott, *Beale's Archives of Medicine*, 1859, vol. i. p. 209.

as follows: i. The average amount of bile secreted in 24 hours on June 11th and June 13th, was 1960.7 grains of fluid bile; 104.438 grains of solid bile; and 32.864 grains of bile acids. Three grains of calomel were given at 3 o'clock in the afternoon of June 13th. The average of the two days after giving this dose was 1358.1 grains of fluid bile; 70.4 grains of solid bile, and 26.2 grains of bile acids. Less food was, however, taken after the calomel.

ii. The bile of 24 hours collected on June 16th was 1639.9 grains in weight: solid bile, 77.599 grains; the bile acids, 12.5 grains. On this day six grains of calomel were given at half past eleven in the morning; the bile collected on June 17th was 518.7 grains in weight; solid bile, 42.18 grains: the bile acids 10.4 grains. No food, however, but 12 ounces of milk was taken on June 17th, and only 9 ounces of water on June 18th, yet the amount of bile collected on June 19th was 817.7 grains of fluid bile; 61.7 grains of solid bile; and 27.486 grains of the bile acids. Thus it would seem that merely withholding food would not cause such a great decrease as was seen after the calomel.

iii. On the 2nd and 3rd of July, the average quantity of bile for 24 hours was 3044.8 grains of fluid bile; 139.2 grains of solid bile, and 61.9 grains of bile acids. The third dose of calomel, 10 grains in amount, was given at half past four on July 3rd. The average for 24 hours of the bile passed on July 4th and 5th was 2720.9 grains of fluid bile; 135.4 grains of solid bile; and 70.6 grains of the bile acids. The bile acids, it should be noted, were thus increased.

iv. On the 6th and 7th of July, the average quantity of bile for 24 hours was 2658.6 grains of fluid bile; 117.7 grains of solid bile; 57.4 grains of bile acids. Twelve grains of calomel were given at six o'clock in the afternoon of July 7th. The average of July 8th

and 9th for 24 hours was 1728·9 grains of fluid bile ; 85·6 grains of solid bile ; and 45·9 grains of the bile acids.

The Edinburgh Committee praise Dr. Scott for the careful and scientific way in which he has made these experiments, and I think every one who is able to judge of these matters will more than agree with them on this point. They, however, look upon Dr. Scott's observations as valuable contributions to the study of the influence of calomel on the bile rather than data which in themselves warrant any conclusion. They think that the diminution of the bile is not nearly so great as Dr. Scott would make out.

The Edinburgh Committee, appointed by the British Association for the Advancement of Science to investigate the action of mercury on the bile, began their work by questioning if mercury have the same action on dogs as on man. The injection of corrosive sublimate under the skin of dogs brought out the same symptoms as in man ; salivation, discharge of mucus from the nostrils, foetid breath, and ulceration of the gums. All these symptoms appeared whether a biliary fistula had or had not been established. In all the dogs without a biliary fistula profuse diarrhoea was caused. In the dogs with biliary fistula, diarrhoea was slight in one and entirely absent in the other two. The Committee conclude that the action of mercury on the dog is the same as that on man.

Their next experiments were on the action of blue pill. In one dog, the mean amount of bile escaping from a biliary fistula in 24 hours from June 11th to June 19th was 119·76 grammes, of which 7·622 grammes were bile solids and 1·259 gramme inorganic salts ;* from June 29th to July 4th, the mean was 131·31 grammes, of which 4·71 grammes were bile solids ;

* By inorganic salts is meant the residue left after incineration of the bile.

and 1.343 gramme inorganic salts. From July 9th to July 17th 5 grains of blue pill were given daily, and the mean for 24 hours during this time was 127.6 grammes of fluid bile, of which 5.16 grammes were solids, and 1.38 gramme inorganic salts. Another series of observations was made, but accidents rendered it valueless.

Much the same results were attained with calomel. During 7 days from Sept. 21st to Sept. 27th the mean of fluid bile flowing from a fistula was 82.46 grammes, of which 5.31 grammes were solids, and 1.042 gramme inorganic salts. From Sept. 28th to Oct. 3rd, calomel was given to the dog in doses of two grains, once, twice, or three times a day. The mean of fluid bile during the first four days was 60.02 grammes. The effect of the calomel on the health of the dog was very decided, and it died on Oct. 5th.

It was then determined to note the effect of small doses of calomel frequently repeated. The mean of four days before the calomel was given was 70.62 grammes of fluid bile; of which 3.792 grammes were solids, and 0.83 gramme inorganic salts. On Oct. 30th seven pills were given; each pill held $\frac{1}{12}$ grain of calomel. An hour passed between the giving of each pill. In the same way 14 pills were given on Nov. 1st, and 6 pills on Nov. 2nd. The calomel rapidly acted on the health, and the dog died on Nov. 3, food having been refused for three days before. But no change in the amount of bile was seen: the mean of the four days after the calomel was almost the same as the mean of the four days before: 70.32 grammes of fluid bile, 3.732 of solids, and 0.89 gramme of inorganic salts.

Another experiment was made with calomel in doses large enough to cause purging. The average of six days before the calomel was given was 357.4 grammes of fluid bile, 13.11 grammes of solids, and 3.12 grammes

of bile salts. Ten grains of blue pill were then given to the dog, and the three following days ten grains of calomel were given daily. The two first doses of mercury caused slight purging; the two last caused marked purging. During these four days there was an undoubted decrease of the amount of bile. The mean was 272.67 grammes of fluid bile; 7.78 grammes of solids; and 2.06 grammes of inorganic salts. The health of the animal was unaffected by the purging.

Some experiments were also made with corrosive sublimate. The mean, during three days before the corrosive sublimate was given, was 105.4 grammes of fluid bile; 4.144 grammes of solids; and .948 gramme of inorganic salts. On the 4th day, two doses, of $\frac{4}{8}$ grain of corrosive sublimate were injected under the skin of the dog, the first at 1 p.m., the second at 9 a.m. the next day. The bile secreted in the 24 hours under the influence of this corrosive sublimate was 78 grammes; the bile solids were 3.178 grammes and the inorganic salts .717 gramme. The dog died during the night after the second dose, having shown general tremor, purging with bloody fluid stools, and discharge from the nose.

The next trial was with smaller doses. The mean of three days was 127.15 grammes of fluid bile; 6.43 grammes of solids, and 1.03 gramme of inorganic salts. For ten days corrosive sublimate was injected under the skin; the first three days $\frac{1}{8}$ grain in single doses daily; the remaining seven days, twice daily, save that the last dose injected was $\frac{1}{8}$ grain. The mean during these ten days was of fluid bile, 113.8 grammes; of solids, 5.972 grammes; and of inorganic salts, .99 gramme. The health of the animal did not suffer and its weight continued the same. $\frac{1}{8}$ grain was given twice on the 11th day and once on the 12th, and observations were suspended as the dog was then suffering

much from the effects of the drug. The fluid bile fell to a fourth, and the bile-solids to a third, of what they had been the day before.

Another experiment of the same kind was carried out with results very much the same.

The Committee conclude that blue pill, calomel, and corrosive sublimate, "when given to dogs in either small, gradually augmented, or in large doses, do not increase the biliary secretion; they do not even influence it so long as neither purgation nor impairment of health are (*sic*) produced, but they diminish it as soon as they do either or both."*

Up to this point, the experiments which have been spoken of have been made on the following plan: a biliary fistula has been set up, and after the dog had regained its health, the amount of bile passed in 24 hours has been collected, in various ways, that used by Dr. Scott being the most accurate, and a mean struck, believed to represent that of health: the drug to be tested, in most cases mercury, was then given; and the amount of bile passed, day by day, measured and compared with that given before the drug. The experiments of Röhrig and Dr. Rutherford have all been made somewhat differently.

In Röhrig's plan, the dogs and rabbits were made motionless by woorara, and artificial respiration set up. This last was carried on with the greatest regularity, as it was found that slight changes in the breathing led also to changes in the manner of expulsion of the bile. A glass cannula was then inserted into the common duct, the gall-bladder pressed upon so as to fill the cannula with bile, and the cystic duct clamped to prevent the return of bile into the gall-bladder. In this

* Edinburgh Committee, *Report of the Thirty-eighth Meeting of the British Association for the Advancement of Science; held at Norwich in August, 1868.* London, 1869, p. 222.

way all the bile which passed down the hepatic duct escaped at the end of the cannula, and the quickness or slowness of the secretion was judged of by counting the seconds between the fall of each drop of bile from the end of the cannula.

Röhrig says, that with large doses of calomel (20 grains for a dog) it is sometimes, but rarely, seen that the bile will again begin to flow after it have completely stopped; and that the drug is able to increase the secretion, after a certain fashion, if it have only fallen off in amount. He speaks of two cases in which the secretion had completely left off; 20 grains of calomel in emulsion were then given; and in two hours the bile had again begun to flow at the rate of one drop for every 120 or 130 strokes of the metronome; at the end of another hour, there was one drop in 85 or 79 strokes; but in half an hour's time the secretion became less, and in 35 minutes had altogether stopped. Calomel may be more trusted if it be desired only to increase a flow of bile which has not entirely ceased; and in this respect the drug gives much the same results as sulphate of magnesia, which, according to Röhrig, acts feebly on the secretion of bile; but his single experiment on this point does not seem to me worthy of very great attention.*

Dr. Rutherford modified Röhrig's process so far that the amount of secretion was not measured by the time that passed between the fall of each drop but by the amount of secretion itself, received in a finely graduated tube. The trials were always made on dogs which had fasted for 18 hours, and which were motionless with woorara.† Several experiments were made with mercurial salts. Ten grains of calomel in 7 C.C.

* Röhrig, Stricker's *Medizinische Jahrbücher*, Wien, 1873, p. 254.

† Rutherford and Vignal, *Experiments on the Biliary Secretion of the Dog*, p. 1. Report attached to the *British Medical Journal*, 1875, vol. ii.

of water were injected into the duodenum of a dog weighing 19·1 kilogrammes, and an increase of the biliary secretion followed. For two hours before the calomel, the amount of bile secreted was 3·35 C.C., in two hours immediately after, it was 4·25 C.C. After a second dose of ten grains of calomel, the secretion again rose to 4·72 C.C. in two hours. In three other experiments with calomel, no increase was seen; in one, there was a decrease; in the second, no increase; in the third, three grains only were given; and in three-quarters of an hour after the first dose, an increase took place; but the value of this increase is doubtful, as quite as great an increase had taken place before the calomel was given. Two more doses of three grains were given, and were followed by a decrease of the amount of the bile and of the percentage of solids.*

Later on in the series of experiments, the calomel was given mixed with bile. Calomel is said to be slightly soluble in this humour; and it might be asserted that, owing to the absence of bile from the intestines, the calomel could no longer act, as it had no longer a solvent. In two experiments the calomel, even when mixed with bile, and placed in the duodenum, did not increase the amount of bile.

It was suggested to Professor Rutherford that, the calomel being introduced into the duodenum, the action of the gastric juice was avoided; and that the action of the gastric juice might be to convert the calomel into corrosive sublimate. It was found, in fact, that five grains of calomel, if digested for 17 hours in a 2 *per mille* solution of hydrochloric acid, at the temperature of the human stomach, would yield $\frac{1}{35}$ grain of corrosive sublimate. Some experiments were accordingly made with corrosive sublimate. In the first, a dog, weighing 8·8 kilogrammes, had $\frac{1}{20}$ grain, $\frac{1}{15}$, $\frac{1}{15}$, $\frac{1}{20}$, $\frac{1}{15}$,

* Rutherford and Vignal, *op. cit.* p. 14.

$\frac{1}{10}$ grain of corrosive sublimate, dissolved in 3 C.C. of water, injected into the duodenum at intervals. Altogether $\frac{2}{5}$ grain were given. A slight increase followed the fourth dose ; but the result of the whole experiment may be looked upon as negative. But in the next two experiments quite a different result appeared. A little bile was added to the solution of corrosive sublimate. After the injection of this body, in $\frac{1}{16}$ grain doses, into the duodenum of dogs weighing 16 and 17 kilogrammes, the amount of bile secreted rose to a surprising height, from $\cdot 17$ or $\cdot 20$ the kilogramme of weight, to $\cdot 47$ or $\cdot 55$ the kilogramme. Two more experiments were made with a mixture of corrosive sublimate and calomel in bile. In the first of these there was some increase, and in the second, an immense rise in the quantity of bile secreted. A final experiment with corrosive sublimate alone was made ; but the results, from the great variations of the amount, whether corrosive sublimate were given or not, cannot be looked upon as proving much.*

Seeing, then, that corrosive sublimate has a decided action on the secretion of bile, and that some part at all events, of calomel, exposed to the action of hydrochloric acid of the same strength as the gastric juice, is turned into corrosive sublimate, it becomes a matter of speculation whether calomel might not, if introduced into the stomach, act on the liver by a partial conversion into corrosive sublimate. And I fear I must here state my belief that I do not think this question has been completely answered. Dr. Rutherford injected through the gastric wall of a dog five grains of calomel, and says "the result of the experiment was entirely negative, both as regards the liver and intestinal glands," that is, no purgative action was caused by

* Rutherford and Vignal, *op. cit.* p. 79, attached to the *British Med. Journal* for July 7, 1877.

the calomel. It will be admitted on all hands that calomel commonly has a purgative action; but if no purging was caused in this case, why should the effect on the liver, if any, be seen? After the death of the dog, the calomel was found "apparently unchanged, enveloped in the mucus of the stomach." I am informed that, in the present state of chemistry, the estimation of mercurial salts in organic fluids is attended with extraordinary difficulties, and Dr. Rutherford does not seem to have attempted an estimation of this sort. But until this shall have been done, I think it will hardly be possible to deny positively that the action of calomel is not accompanied by some change in its chemical properties.*

Leaving now the discussion of the action of mercury as a cholagogue, unsatisfactory as this may seem, the influence of other drugs upon the secretion of the bile will be considered. It will be convenient to take these medicines in some order; and the results of Dr. Rutherford's observations will be followed as a guide; not only because he has made trial of a far larger number of drugs than any other observer, but because his results, from the great care and improved methods employed, are more worthy of attention than those of any who have gone before him.

i. The bodies which have no apparent action upon the secretion of bile are the following :

Morphia	Dilute Alcohol
Hyoscyamus	Bicarbonate of Soda
Atropia	Iodide of Potassium
Tannic Acid	

Morphia.—Röhrig injected 1·6 C.C. of *tinctura thebaica* into the jugular vein of a dog; the secretion of

* See a very interesting research by Carl Voit on the manner in which the insoluble calomel is absorbed and acts. (*Phys.-chem. Untersuchungen*, Augsburg, 1857, p. 49.)

bile had fallen to one drop in 62 seconds, as the dog had been two hours under observation, and was very weak. Nevertheless, the secretion began at once to rise, and in twenty minutes was one drop in 26 seconds. A like rise was seen after the injection of 4.8 C.C. into the bowel.* Dr. Rutherford came to the conclusion that three grains of morphia, injected into the bowel had no influence on the secretion of bile.

Hyoscyamus also has no noteworthy effect on the secretion of bile.

Neither of these bodies interferes with the action of a cholagogue like salicylate of soda; when the salicylate was given after morphia or hyoscyamus, the secretion of bile rose at once to as high a point as if no morphia or hyoscyamus had been given.†

Atropia. It is believed by practitioners that belladonna decreases the secretion of the milk and sweat. Dr. Rutherford therefore thought it well worth while to test its action on the bile. It was found, however, to have no immediate action, neither increasing nor decreasing the secretion; and the same result was attained by Laffter, in Heidenhain's laboratory, before the year 1873.‡ But as atropia antagonises the action of calabar bean in other parts, so it antagonises its action on the liver; calabar bean increasing the amount of bile as well as of the saliva, tears and *succus entericus*.§

Carbonate of Soda early attracted notice; from the same reason, apparently, that mercury did: it had been found useful in the bilious state, that is, acute or chronic gastric catarrh, and so, by a natural blunder, connecting bilious disorders with the bile, carbonate of soda was thought to have some special action on the bile.

* Röhrig, *op. cit.* p. 272.

† Rutherford, *British Medical Journal*, 1879, vol. i. p. 135.

‡ Th. Laffter, *Versuche zur Physiologie der Gallensecretion*, Diss. Inaug. Breslau, 1873, p. 22. He came to no trustworthy results with calabar bean.

§ Rutherford, *British Med. Journal*, 1878, vol. ii. pp. 861 and 909.

Hermann Nasse added on the first day to the food of the dog on whom he had made a biliary fistula 2.5 grammes (37 grains) of carbonate of soda. On the third and fourth days, 1.25 gramme (about 18 grains) was given. On the three following days the food and carbonate of soda were increased by one half. During the first days when the large doses were given, the amount both of fluid and solid bile was much decreased.* Röhrig also finds that carbonate of soda causes a decrease for several hours of the amount of bile secreted both in rabbits and dogs.† Dr. Rutherford, on the other hand, found that bicarbonate of soda feebly increased the amount of bile secreted. In his two experiments the amount of bile slightly rose after each dose.‡

ii. It was formerly thought that the drugs which caused purging would also increase the secretion of bile, probably because it was believed that unchanged bile appeared in the stools. An ingenious anonymous writer§ explains the good effects of purging by the following hypothesis: the bile, if we follow Schiff's observations, is continually making a circulation between the liver and the intestines: first being poured into the duodenum, then absorbed from the intestines into the blood, then carried by the blood to the liver again, and by this organ again excreted into the duodenum: purgatives act by breaking this vicious circle; they hurry the bile through the intestines, not letting it rest long enough in the intestine to be absorbed, and so the patient is relieved from the excess of bile.

It was stated by Röhrig that purging by itself increased the amount of bile ;|| but the Edinburgh

* H. Nasse, *op. cit.* p. 9.

† Röhrig, *op. cit.* p. 271.

‡ Rutherford, *British Med. Journal*, 1879, vol. i. p. 105.

§ Probably Dr. Lauder Brunton, *British Med. Journal*, 1873, vol. i. p. 15.

|| Röhrig, *op. cit.* p. 249.

Committee* and Dr Rutherford§ came to the opposite conclusion; and in this matter, as in many others, I should be inclined to accept their results rather than those of Röhrig. The drugs, which increase the intestinal fluid, but have no action on the bile, are:

Calomel	Castor Oil
Gamboge	Chloride of Ammonia
Sulphate of Magnesia	Menispermin
Sulphate of Manganese	

Sulphate of Magnesia. This salt is said by Röhrig to have a slight influence on the bile, raising the secretion from one drop in 98 seconds to one in 34.† Dr. Rutherford, however, finds that sulphate of magnesia has no action as a cholagogue, but that the secretion of bile is diminished when purging comes on.§

Castor Oil. Röhrig|| and Rutherford¶ agree that Castor oil is almost without influence upon the amount of bile secreted.

iii. The only body the primary action of which is known to cause a decreased secretion of bile is:

Acetate of Lead. Both Röhrig and Dr. Rutherford hold that this has a direct depressing effect upon the secretion of bile. In Röhrig's hands it was noted that when acetate of lead was injected into the intestine of a dog the secretion fell from one drop in 21 seconds to one in 50 or more.** Dr. Rutherford injected fifty grains of acetate of lead, in doses of ten grains each, into the duodenum of a dog and found a decided fall after every dose. The fall was not due to the liver being exhausted; for a dose of salicylate of soda caused the amount of bile to rise to a point higher than it was at the beginning of the experiment.††

* Edinburgh Committee, *op. cit.* 229. † Rutherford and Vignal, *op. cit.* p. 17.

‡ Röhrig, *op. cit.* p. 254.

§ Rutherford and Vignal, *op. cit.* p. 73.

|| Röhrig, *op. cit.* p. 255.

¶ Rutherford and Vignal, *op. cit.* p. 16.

** Röhrig, *op. cit.* p. 270.

†† Rutherford, *Brit. Med. Journal*, 1878, vol. ii. p. 945.

iv. The following drugs are able feebly to raise the secretion of bile :

Croton Oil	Chloride of Sodium
Senna	Bicarbonate of Potash
Taraxacum	Jaborandi
Scammony	

Croton oil. Röhrig held croton oil to be one of the most active cholagogues ; and it stands at the head of his list. A "teaspoonful," diluted with olive oil and thrown into the duodenum, called forth in an hour and a half an active secretion of bile, so that one drop fell from the cannula every three seconds. In other experiments the bile was very viscid and the drops could not be counted.* With smaller doses, Dr. Rutherford found different appearances. After fifteen grains of croton oil (about 30 drops,) diluted with sixty minims of almond oil, were injected, a fall took place ; with six grains, no decrease or increase ; with three grains, a decided increase.†

Senna was found by Röhrig to have an active effect on the secretion of bile. After a dose of 15 grammes in 150 C.C. of fluid, the bile, from dropping once in every 60 seconds began in an hour to drop once in 4 to 5, although this great rapidity lasted but a short time and was followed later on by complete stopping of the secretion.‡ Dr. Rutherford, however, found very little change in the secretion before and after the giving of senna in three experiments ; and if any, the bile contained less solids.§

Taraxacum. This drug was found by the Edinburgh Committee to be tolerably inert. They report that doses of the solid extract varying from 60 to 240 grains had no influence upon the bile nor the health of the dogs ; nor did they cause purging.|| Dr. Rutherford's further experiments agree with this statement.¶

* Röhrig, *op. cit.* p. 250.

† Rutherford and Vignal, *op. cit.* p. 3.

‡ Röhrig, *op. cit.* p. 254.

§ Rutherford and Vignal, *op. cit.* p. 10.

|| Edinburgh Committee, *op. cit.* p. 229. ¶ Rutherford and Vignal, *op. cit.* p. 13.

Chloride of Sodium. Dr. Rutherford made only one experiment with this drug, four doses of 120 grains each being injected into the duodenum. The amount of bile was very feebly increased.*

v. The following are the bodies which markedly increase the secretion of bile :

Aloes	Corrosive Sublimate
Podophyllin	Muscarin
Rhubarb	Nicotin
Colchicum	Calabar Bean
Colocynth	Euonymin
Jalap	Sanguinarin
Ipecacuanha	Iridin
Benzoates	Leptandria
Salicylates	Baptisin
Sulphates of Soda and Potash	Phytolaccin
Phosphates of Soda and Ammonia	Hydrastin
Dilute Nitrohydrochloric Acid	Juglandin

Aloes. After mercury, the preparations of aloes have received most attention from different observers. Kölliker and Müller gave one of their dogs one grain of extract of aloes on one day, and two grains on the following, but they hardly noted any change in the amount of bile daily secreted.† Röhrig tested, with his method, the action of aloes on a dog and a rabbit. No details are given of the experiment on the dog, in which the action of aloes is said to resemble that of jalap. In a rabbit, 3 grammes of aloes dissolved in 7.5 grammes of water were injected into the small intestine. In 70 minutes, the secretion of bile, which had ceased before the solution of aloes was given, began again, 79 to 77 seconds passing between the fall of each drop ; an hour after this, 26 to 13 seconds only between each drop ; in a short time the secretion began to fall off, and in an hour had completely stopped.‡

* Rutherford, *Brit. Med. Journal*, 1879, vol. i. p. 71.

† Kölliker and Müller, *op. cit.* p. 231.

‡ Röhrig, *op. cit.* p. 252.

Dr. Rutherford also found a great increase of bile, marked in 30 minutes after aloes had been given. Though the bile was rendered more watery, yet a greater amount of solids was excreted. The experiments were made on two dogs into whose duodenum sixty grains of aqueous extract of Socotrine aloes in watery solution were injected.*

Podophyllin. The action of this drug upon dogs with biliary fistulæ was first investigated by the Edinburgh Committee. They report that doses of podophyllin, varying from 2 to 8 grains, given to dogs, caused a decrease of the solid bile, whether purging came on or not. Doses which caused purging also caused a decrease in the solid and fluid parts of the bile.† This is the only part of the report on podophyllin which coincides with the experiments made by Dr. Rutherford later on. On the contrary, he found that podophyllin injected into the duodenum increased the flow of bile in seven experiments, and that this flow of bile is greater when bile also is present in the duodenum. The mucous membrane of the intestine was usually much reddened.‡

Rhubarb was found by Röhrig to raise the secretion of bile from one drop in every 92 seconds to as much as one drop in every 9 seconds.§ Dr. Rutherford also found rhubarb a remarkable stimulant to the secretion of bile. The injection of rhubarb into the duodenum was always followed by a remarkable rise in the amount of bile, the composition of which remained unchanged.¶

Colocynth. Röhrig placed colocynth near the head of his list of cholagogues; under its influence he saw that a drop of bile fell from the cannula every two or three seconds.* Dr. Rutherford finds that colocynth

* Rutherford and Vignal, *op. cit.* p. 7. † Edinburgh Committee, *op. cit.* p. 229.

‡ Rutherford and Vignal, *op. cit.* p. 8. § Röhrig, *op. cit.* p. 253.

¶ Rutherford and Vignal, *op. cit.* p. 4. ¶ Röhrig, *op. cit.* p. 252.

has considerable influence in increasing the secretion of the bile, although it does not seem to be worthy of the very high place given to it by Röhrig. Colocynth increases both the fluid and solid parts of the bile.*

Jalap. Next to colocynth as a cholagogue Röhrig set jalap† and Rutherford agrees with him that the drug is a considerable stimulant to the secretion of bile, though its chief action is on the intestinal glands.‡

Benzoates and Salicylates. The study of the physiological action of these bodies upon the liver is interesting. In their chemical composition they are allied. They both combine with glycocoll, the base of one of the bile acids, to form hippuric and salicyluric acid.

Benzoic acid has been long employed in the treatment of jaundice, and it was made the subject of some experiments by Kühne about twenty years ago. He thought that in jaundice benzoic acid passed out by the urine unaltered instead of combining with glycocoll to pass out as hippuric acid.§ Kühne's theory was, however, soon disproved, as the presence of the benzoic acid in the urine was found to be due to the decomposition by putrefaction of the hippuric acid. It is, therefore, noteworthy that both benzoates and salicylates greatly increase the secretion of bile by the liver, and are among the most active of the drugs investigated by Dr. Rutherford; and his results on this point are perhaps the most interesting to the physiologist of all that he has published. Benzoic acid, itself, apparently owing to its insolubility, has but slight action on the bile, while the soda and ammonia salts at once raise the amount secreted.||

Muscarin. Prevost says that a few milligrammes of

* Rutherford and Vignal, *op. cit.* p. 69.

† Röhrig, *op. cit.* p. 252.

‡ Rutherford and Vignal, *op. cit.* p. 72.

§ Kühne, *Arch. f. path. Anat.* 1858, Bd. xiv. p. 318.

|| Rutherford, *British Medical Journal*, 1879, vol. i. p. 69.

muscarin injected into a vein cause a notable increase of the bile in a dog. Atropia, however, antagonises this effect.*

Nicotin. Laffter found, in Heidenhain's laboratory, that 3 drops of nicotin in 50 grammes of water, injected into the jugular vein of a dog, cause an immediate but short increase of the bile. This appearance was thought due to the contraction of the ducts, and consequent expulsion of bile.†

Euonymin, Iridin, etc. The eight drugs mentioned last on the list come from American sources, and iridin and euonymin are specially active in increasing the secretion of bile, as will be seen by the following table. This table has been borrowed from Dr. Rutherford, and he remarks, that a drug may be looked upon as a powerful cholagogue if it raise the hourly secretion of bile for every kilogramme of body weight to 0.4 C.C.

Drug.	Total dose in grains.	Dose in grains for kilogramme of body weight.	Secretion of bile for kilogramme of body-weight: an hour.	
			Before. C.C.	After. C.C.
Normal secretion of bile during the influence of small doses of woorara }			0'35	
			0'25	
			0'15	
Podophyllin	6 without bile	0'9	0'04	0'47
"	4 with "	0'23	0'52	1'01
Aloes	60 without "	6'9	0'34	0'69
"	60 " "	12'0	0'26	'93
Rhubarb	68 " "	3'06	0'17	0'32
Colchicum	60 " "	2'5	0'13	0'45
Euonymin	5 with "	0'26	0'25	0'47
"	5 " "	0'21	0'07	0'46
Sanguinarin	3 " "	0'11	0'16	0'30
"	1 " "	0'05	0'12	0'40
Iridin	5 " "	0'22	0'22	0'53
"	5 " "	0'92	0'16	0'63
Leptandria	18 " "	1'4	0'08	0'31
Ipecacuanha	60 " "	2'2	0'24	0'55
"	3 " "	0'49	0'18	0'38
Colocynth	14 " "	0'53	0'20	0'45
"	7 " "	0'4	0'16	0'27
Jalap	30 " "	1'2	0'16	0'29
Sodium sulphate	508 " "	32'3	0'25	0'38

* Prevost, *Comptes rendus*, 1874, t. lxxix. p. 381.

† Laffter, *Versuche zur Physiologie der Gallensecretion*, Diss. Inaug. Breslau, 1873, p. 24.

excitement of the liver. Something like this is seen in the action of sialagogues, which cause a great flow of saliva by acting on the buccal mucous membrane. Against this theory is the fact that those drugs which most actively excite the intestinal mucous membrane do not excite the secretion of the liver; while the most active cholagogues are those which have no influence on the mucous membrane: (ii.) that these cholagogues increase the flow of blood through the liver; a theory thought to be opposed to the fact that an increased flow of blood to the intestines is not followed by increased secretion of bile. But an excess of blood in the intestines is followed, not always by an excess of blood, but sometimes by a want of blood, in the liver: or (iii.) that these cholagogues have a direct action upon the cells or nerves of the liver, a theory to which Dr. Rutherford is himself inclined.

It has been seen that the wish to increase the amount of bile excreted by the liver comes of a most venerable antiquity; but it may now be asked: in what diseases or in what states would good be done to a patient if the amount of bile poured into the duodenum were increased? It seems to me that it would be judicious to put aside at once all organic diseases of the liver, such as cirrhosis, amyloid degeneration, and the like; for in them the same kind of evil would follow the use of a stimulant to the liver, as of certain diuretics in Bright's disease; and one of the first rules of medicine, to give diseased parts rest, would be broken. Then in cases of jaundice, it would surely be undesirable to attempt to increase the secretion of bile; for the bile passages being already over-filled, harm would be done by pouring fresh bile into them. Then comes the long list of disorders which the public love to think due to "the bile," and call "biliousness," the symptoms of which are really due to a catarrhal state of the gastro-

duodenal mucous membrane, as will be seen in the chapter on bilious disorders. Would an increased secretion of bile be good in a bilious disorder, that is, gastro-duodenal catarrh? I cannot appeal to experience on this matter; but if it be safe to hazard a conjecture beforehand, it would seem improbable that the pouring of a fluid like bile over an inflamed mucous membrane would relieve it; and an effectual remedy is already known in a single mercurial purge, followed by a gentle alkaline course. Dr. Rutherford says he has found very decided benefit from administering four grains of iridin at bedtime in cases of "biliousness;" the patients awaking in the morning and finding the headache and malaise gone, and the yellow tongue clean; and he also recommends that a dose of Püllna water be taken after the iridin, and that iridin be not taken oftener than once a week, as it leaves a somewhat depressant effect behind it. Instead of iridin, Dr. Rutherford would seem rather inclined to favour euonymin in two-grain doses, and says that he has "been much struck with the success of euonymin in functional hepatic derangement, in several persons who had tried nearly all the commonly used cholagogues with varying and often very limited success."*

There is one state in which I can well imagine that an increase of bile might be useful; and that is at the end of an attack of jaundice when the stools have begun to shew some appearances of returning colour, but

* Rutherford, *British Medical Journal*, 1879, vol. i. p. 178.

I know that functional hepatic derangement is often talked about; and I fear that some will think it a disgraceful confession when I own my entire and complete ignorance of this pathological state. I have never met with it in the *post-mortem* room and I do not know how it can be recognised during life. Precise and accurate information as to the clinical state, called by some practitioners congestion of the liver, torpor of the liver, or sluggish action of the liver, is also wanting; and also the appearances seen after death in these diseases; or if they do not prove fatal, the grounds on which the symptoms are linked to a disturbance in the functions of the liver.

the conjunctiva, skin, and urine of the patient still remain yellow. In this case a stimulus to the secretion of bile may possibly be of much use; and in former times the benzoates have been successfully used for this purpose.

If the office of the bile were better known, it would be easier to say in what states an increase of this humour may be wished for. Modern physiology seems rather to be on the way of returning to the opinion of Aristotle that the bile is an excrement, though not an immediate excrement, as great part of it is again absorbed into the blood. The bile is now thought to have little influence on the digestion of the food. But it may hereafter be proved to play an important part in the metamorphosis of the tissues; and then the amount of bile secreted will enter into the calculations of the scientific physician. Until Dr. Rutherford began his series of researches, the prescriber of drugs was altogether without trustworthy knowledge, whenever he wished to increase the amount of bile secreted. There was nothing to guide him but the tradition of the power of calomel. Now there is a certain foundation to build on, and Dr. Rutherford's results and method are the beginning of a new and reasonable system of hepatic therapeutics.

Though somewhat foreign to the subject of this chapter, yet it may be convenient here to consider whether any drugs have the property of causing unchanged bile to appear in the stools. It will, I suppose, be granted by the chemists that in health the unaltered bile pigments cannot be found in the fæces. Yet there can be no doubt that the colour of the fæces in health is due to the presence of the bile, however much the pigments may be changed; for if the bile duct of an animal be tied, or if in man disease obstruct the duct, the fæces at once lose their

natural colour and become white. But between acknowledging that the colour of the fæces in health is due to the bile, and that all the variations in colour seen in disease are due to the bile, there is a wide distance. Formerly a high colour was thought evidence of increase of bile in the fæces. Purgatives often bring away high-coloured stools; therefore purgatives increase the amount of bile in the fæces.

This reasoning should, however, long have been abandoned. It is well known that many drugs given by the mouth cause the fæces to become black; for example, charcoal, iron, bismuth; and that the presence of blood gave a black colour to the stools was known to Hippocrates.

The want of colour in the fæces is almost universally set down to a decrease in the secretion of bile. But I should like to point out that of this there is no evidence. The absence of bile is, no doubt, the cause of the white stools in jaundice; but it would be highly imprudent to assert that it is the only cause of want of colour in every disease. In many kinds of brutes, the fæces are grey or even white in health, and in some of these, as in the dog, there is evidence that the liver is as active as in man. The colour of the fæces, then, is not due to the want of the secretion of bile; it is rather more likely to be due to the absorption of the bile after it have passed into the intestine. Then on certain diet, as milk, the stools often become light coloured; yet there is no evidence of a decreased secretion of bile, or of an increased absorption of bile from the intestine. It is easy to imagine a cause for this lack of colour, but there is no certain knowledge about it.

In judging of the presence or absence of bile in the fæces, chemical analysis is, in my opinion, the only trustworthy guide.

It is well known that calomel, in purgative doses,

brings away stools of a peculiar green colour, compared to that of spinach. Michéa attempted by a chemical analysis to prove that this colour is due to the presence of bile. He discarded Pettenkofer's test, as he found it troublesome to apply; but availed himself of the well-known reaction of the bile pigments with nitric acid. He found no play of colours in the stools of healthy men and women; but in one case of *embarras gastrique* out of three, the action was distinct enough in the vomited matters and green stools. Calomel was given to eight persons suffering from constipation: in four, green stools were passed; and in two of these four, nitric acid detected the presence of bile. Sulphate and phosphate of soda, jalap, and castor oil were given, but the stools had not the green colour of calomel stools, nor did nitric acid give the peculiar reaction.* Radziejewski, on the other hand, gave calomel to a dog with a biliary fistula, in which, therefore, no bile could enter the intestine; and saw the accustomed loose stools of a green colour, but in these no bile pigment could be found. It was further shown by Radziejewski that undecomposed bile is but rarely found in the fæces after the action of purgatives of any sort; out of nearly forty experiments on dogs, undecomposed bile was only found four times, after calomel, castor oil, senna, and croton oil, and even then the reaction was somewhat doubtful.† The appearance of the fæces was found in no way to correspond with the results of the chemical analysis. They were often green, and yet gave no reaction with Gmelin's test.

The cause of the green colour of the stools is not well made out. It may very possibly be due to some compound of mercury; for the statement that mercury is not to be found in the fæces cannot be maintained

* Michéa, *Union méd.* 1848, t. ii. p. 495.

† Radziejewski, *Arch. f. Anat. Phys. u.s.w.* 1870, p. 37.

after the observations of Saikowski,* and of Mayençon and Bergeret,† who found that the fæces as well as the urine were the chief vehicles by which mercury leaves the body. A green colour is also seen after some other purgatives besides mercury; for example, in the stools of those who make use of the Carlsbad and Marienbad waters.

Drugs which pass into the bile. Several isolated observations were made before 1858, on the drugs which are found in the bile after being introduced into the œconomy; but it was Mosler who first carried out a definite research on this point. Biliary fistulæ were made in dogs; and in a week or more, the bodies to be tested were either injected into the veins or else given by the mouth.

Albumen was the first body to which attention was directed. Mosler found that it was not a natural constituent of the bile of dogs. On injecting 135 C.C. of warm water into the crural vein of a dog, albumen appeared in the bile in from 2 to 4 hours after the injection; the albumen decreased in amount in 6 to 7 hours after; in 8 hours, only a trace was found; and in 8 to 10 hours, none. The urine showed albumen even half an hour after the injection.

Mosler says nothing of the way in which the albumen was looked for. It is known that the bile acid salts have the property of coagulating albumen.

Mosler satisfied himself that no grape sugar was present in the bile of dogs in health, and that a great quantity must be present in the blood before it appeared in the bile. After 20, 30, and 40 grammes (300 to 600 grains) had been injected into the crural vein, none could be found in the bile while there was abun-

* Saikowski, *Arch. f. path. Anat.* 1866, Bd. xxxvii. p. 346.

† Mayençon and Bergeret, *Journal de l'Anatomie et de la Physiologie*, 1873, p. 81.

dance in the urine. When 65 to 80 grammes (1000 to 1200 grains) were injected, the dog usually died or was killed ; and after death sugar was found in the contents of the gall-bladder.

Cane sugar appears in the bile, as in the urine, more readily. Only 40 grammes need to be injected into the veins.

One gramme (15 grains) of iodide of potassium given by the mouth could not be detected with certainty the same day in the bile. The next day two grammes (30 grains) of iodide were given, and a distinct reaction was found with starch on the third day. In another experiment, one gramme of iodide was given at 7 in the morning ; and at 3 in the afternoon, the bile gave distinct signs of the presence of iodine ; the bile collected from 3 o'clock to 7 next morning gave no reaction.

Six grammes (about 90 grains) of nitre, given by the mouth, did not cause the bile to show a reaction indicative of the presence of nitrates.

For three days a dog was given twelve grains of sulphate of copper every day, in pills of two grains each every two hours. A trace of copper was found in the bile on the first two days ; on the third, however, there could be no doubt about its presence, both in the bile and urine. Mosler thinks that more copper is excreted by the bile than by the urine. Copper, however, would appear to be a constant constituent of bile.

5 and 10 grains of calomel were given by the mouth to a dog ; but no mercury was found in the bile collected within 24 hours. A chemist might, however, have something to say as to the method employed for getting rid of the organic matter of the bile ; it is quite possible that in getting rid of the organic matter, the mercury also disappeared.

Autenrieth and Zeller found mercury in the bile of a dog, in no very great amount, however, who had been

killed by rubbing the metal into the skin. The bile was also singularly thick.* C. E. E. Hoffmann, in his inaugural dissertation at Würzburg in 1854, states that he found no mercury with the microscope in the bile or any other part of the animal, after metallic mercury or blue ointment had been given by the mouth or rubbed in. Hoffmann's experiments were made on several animals, dogs, rabbits, and cats, and on one man.†

Oesterlen rubbed blue ointment into the skin of a cat and also gave the animal the ointment to eat. He found mercury, apparently in the metallic state, in the liver, and in still greater quantity in the fluid green bile.‡

Mayençon and Bergeret used a very delicate test for mercury in their experiments, and they found it in great abundance in the livers of rabbits whom they had poisoned.§ It seems probable that it would also be found in the bile, if looked for with equal care; and the bile may be one of the sources of the mercury found in the stools.

Quinine was given to a dog in two following days in doses of two grains each, so that in two days the dog had about 16 grains given it, that is, more than one gramme. None of this body could be found in urine or bile of the following day. It must be remembered however that it is very hard to recognise the presence of alkaloids in organic fluids.

For two days 10 grains (.66) grm. of benzoic acid

* Autenrieth and Zeller, Reil's *Archiv f. d. Phys.* 1807 and 1808, Bd. viii. p. 255. This increased thickness was also noted by Roche. (*Dict. de med. et de chir. prat.* Paris, 1830, t. iv. p. 114, art. Bile.)

† C. E. E. Hoffmann, *Ueber die Aufnahme von Quecksilber und der Fette in den Kreislauf.* Diss. Inaug. Würzburg 1854. Abstract in Canstatt's *Jahresbericht f.* 1855, Bd. i. p. 80.

‡ Oesterlen, *Arch. f. phys. Heilkunde*, 1843, Bd. ii. p. 536.

§ Mayençon and Bergeret, *Journal de l'Anat. et de la Phys.* 1873, année ix. p. 81. Mercury was found in the greatest abundance in the liver and kidneys.

were given to a dog every two hours. Altogether two drachms were given (about 4 grammes.) Hippuric acid was found in the urine but not in the bile.

Turpentine was also given to the dog: but although the urine showed the characteristic smell of violets, yet the presence of turpentine could not be determined in the bile. The bile had indeed a peculiar resinous smell, but no chemical proofs could be had.* This observation is important in its bearing upon the use of Durande's remedy, who proposed to dissolve biliary calculi by giving through the mouth a mixture of æther and oil of turpentine.

Iron, it is known, is a constant constituent of the bile. In a man who had made a practice of swallowing clasp knives, and thus probably introduced metallic iron into his stomach, Marcet found the iron in the bile increased in amount. In 150 grains of this bile, 0.5 grain of prussian blue was found, while in 150 grains of ordinary bile, only 0.2 grain was found.†

Lead was first found by Heller in the bile of a man who had died of chronic poisoning by lead.‡

Annuschat has made some careful experiments to see if this metal can again be recognised in the bile after being given by the mouth. A biliary fistula was established in fourteen rabbits, and lead was given at various times before the establishment of the fistula. Lead was found in the bile, though in small quantity, in all cases in which the metal had been given shortly before the fistula was set up. When the lead had ceased to be given three or more days before the fistula was established, no lead could be found in the bile, though small quantities could be found in the liver.§

* Friedrich Mosler, *Arch. f. path. Anat.*, 1858, Bd. xiii. p. 29.

† Marcet, *Med. Chir. Trans.* 1823, vol. xii. p. 63.

‡ Heller, *Arch. f. phys. u. path. Chemie*, 1845, p. 322.

§ Alb. Annuschat, *Arch. f. exp. Path.* 1877, Bd. vii. p. 45.

CHAPTER IX.

THE PHYSIOLOGICAL ACTION OF THE BILE.

The bile of animals has been used in medicine from the earliest times. In Hippocrates it enters into the composition of pills and other remedies to be taken by the mouth, as well as of pessaries, suppositories, and applications to wounds. In the book of Tobit, it is used as a lotion for opacities of the cornea,* and Pliny mentions with horror and reprobation that Miletus had proposed human bile for the same purpose.† In these days ox bile has been given in capsules in cases of jaundice; and Röhrig has suggested that in high fever bile acids might be given to bring down the præternatural heat of the body.‡

The physiological action of the bile can hardly be said to have been studied until less than 30 years ago. There are indeed some old experiments by Deidier who injected the bile of patients who had died of the great plague at Marseilles into the veins of dogs, and found that the dogs were speedily killed; when swallowed, the bile did no harm;§ and Magendie shortly states that a gramme of bile rapidly injected into the crural vein will kill an animal in a few moments; but the same

* It is clear that the book of Tobit was written after the Babylonish Captivity; but the latest date given to it by any critic is, I am told, the second century before Christ.

† Plinii *Hist. Nat. Lib.* xxviii. cap. ii. "Miletus oculorum suffusiones felle hominis sanari."

‡ Röhrig, *Arch. d. Heilkunde*, 1863, p. 418.

§ Deidier, *De bile peste emort. exp.* quoted by Bianchi, *Hist. Hepatica*, Genevæ, 1725, Pars iii. p. 804. According to Haller (*Biblioth. Anat.* t. i. p. 808.) these experiments have been published several times; in *Journal Savans*, 1722, and *Phil. Trans.* n. 370, as well as separately at Zürich and Montpellier.

quantity injected slowly, or into the *vena porta*, is harmless.*

Bouisson injected some 120 grammes of bile into the stomach of a dog, and then tied the gullet. After ineffectual efforts at vomiting, a diarrhœa was soon set up. Bouisson thinks this experiment aids the theory that the bile is a natural purgative.† Everyone, however, who has given drugs to dogs, will have noticed that vomiting and purging follow the administration of almost every kind of drug, whatever be its physiological action: so that little weight can be given to this single experiment.

Goupil injected 16 grammes of bile into the saphena of a dog. Shortly after, a general disturbance and languor showed itself, but became less and less intense, and the animal recovered its health without delay. The injection of the same quantity of bile into the portal vein was followed by no symptoms whatever.‡ Bouisson, on the other hand, injected six grammes of human bile, taken from the gall bladder, into the jugular veins of rabbits; in three cases, a sort of tetanic stiffness shortly showed itself, quickly followed by death. On dissection, a distension of the right heart, and thrombosis of the pulmonary artery were found. If, however, the bile were filtered before injection, there was a certain amount of stupor and malaise which completely disappeared within half an hour. Bouisson thought that the action of the bile in the fatal cases was merely mechanical, owing to the suspension of particles in the bile too large to pass the capillaries of the lungs.§ Theodor von Dusch repeated these experiments with filtered bile and found that two rabbits were rapidly killed with tetanus and

* Magendie, *Précis élémentaire de Physiologie*, Paris, 1836, 4e éd. t. ii. p. 259.

† Bouisson, *De la bile*, Montpellier, 1843, p. 56.

‡ Goupil, *Essai sur la physiol. du foie*, Thèse de M. Renaud, Strasbourg, 1838, quoted by Bouisson, *op. cit.* p. 59.

§ Bouisson, *op. cit.* p. 60.

opisthotonos whether the bile were injected into the crural or the jugular vein ; while the injection of filtered bile into the *vena saphena* of a dog was followed only by a few irregular contractions of the muscles, and by vomiting ; and in two days the dog had recovered his health.*

There can be little doubt that some of these cases of severe symptoms following the injection of unfiltered bile are due solely to the mechanical impaction of solid particles in the pulmonary artery. If, however, the bile have been filtered, the cause of death is probably the same, thrombosis of the pulmonary artery ; but the thrombosis is due to the solution of the corpuscles by the bile acids and consequent formation of a clot.†

Johannes Ranke and Sydney found no symptoms follow the injection into the jugular vein of a rabbit of the bile secreted by its own liver.‡ The absence of all appearances is probably due to the small amount of solids in the bile freshly secreted by the liver of vegetable eaters ; and not that the bile secreted by the animal itself has no influence over its own œconomy, as these writers believe.

It will be convenient in further dealing with the physiological action of the bile to consider the experiments in sections corresponding with the chemical constitution of this humour ; the bile acids, bile pigments, and cholestearin. The bile acids show the most active physiological properties, and may therefore be considered first of all.

PHYSIOLOGICAL ACTION OF THE BILE ACIDS.

It has been explained, in speaking of the chemistry of the bile, that Platner's crystallized bile is a mixture of

* Th. von Dusch, *Untersuchungen und Experimente als Beitrag zur Pathogenese des Icterus*, u.s.w. Leipzig, 1854, p. 17.

† See below, Action of the Bile Acids on the Nervous System.

‡ Johannes Ranke, *Die Blutvertheilung und der Thätigkeitswechsel der Organe*, Leipzig, 1871, p. 173.

the soda salts of two acids, taurocholic and glycocholic acid. These two acids differ but little in their physiological action, taurocholic acid being somewhat more active than glycocholic. Feltz and Ritter found that .46 grm. of taurocholate of soda for each kilogramme of animal would cause death, apparently when injected into the blood vessels; of the glycocholate, .64 grm. was needed for each kilogramme; while of the mixture of the two salts (Platner's crystallized bile) .51 grm.* Leyden found that less than a gramme of bile acid salts injected suddenly into the heart would at once cause death in a dog. An injection of 3 or 4 grains into the carotid killed a dog in a few minutes. With injections into the blood done slowly, larger doses, nearly 2 grammes, were needed to kill dogs even in one or two days.†

Johannes Ranke has stated that 15 milligrammes are enough to kill rabbits when injected into the jugular vein. In this mode of death, the bile acid salts kill, not by a specific action on the heart, but by causing a thrombosis of the pulmonary artery.‡ I cannot, from my own observations, confirm Johannes Ranke's statement, as I have found rabbits bear much larger doses with impunity.

In these acids, the active body would seem to be the cholalic acid; it acts upon the heart and dissolves the red corpuscles with energy, while glycocoll and taurin have been found to be almost inert.

Organisms, apparently fungi, were seen in solutions of

* Feltz and Ritter, *Journal de l'Anatomie et de la Physiologie*, 1874, t. x. p. 583. These writers do not expressly say whether the doses were injected under the skin or into the blood; apparently into the blood. Still less do they say into what vessel, whether the jugular or crural vein; and yet this is a matter of some importance.

† Leyden, *Beiträge zur Pathologie des Icterus*, Berlin, 1866, p. 99.

‡ Johannes Ranke, *Die Blutvertheilung und Thätigkeitswechsel der Organe*, Leipzig, 1871, p. 164.

the bile acids in water after the solution had been kept for some weeks. But their growth is not rapid.*

General Experiments: on the frog. If one cubic centimetre of a 10 or 12 *per cent.* solution of Platner's crystallised bile be injected under the skin of a frog, he at once begins to jump about as if much excited. In about five minutes, however, the movements become less active and in ten to twenty minutes the frog is motionless, unless he be touched or made to move. The next appearance is that the hind limbs begin to abide where set by the observer; and with great trouble he draws the legs up when they are extended by observer. He no longer springs but crawls: and if put on his back cannot recover himself. He shows no movements but those of respiration. In a couple of hours or so he is commonly found lying relaxed, no longer in the sitting posture, with pupils contracted, and showing very little or no reflex action.†

These phænomena may appear sooner or later. The frog may die in a few hours; or last on until the third day.

In the advanced stage of the action of the bile acids upon frogs, I have found that electrical irritation of the nerves or muscles was commonly followed by lively contractions; in some instances, however, I have seen no movement follow.

I have also repeated with the same results an experiment first made by Leyden. A frog was put into a vessel holding enough of a 1. *per cent.* solution of bile acids to cover the bottom. The frog was always found dead the next morning, and on examination with the microscope parenchymatous changes were found in the heart and liver.

* See p. 145 on the arrest of putrefaction by the bile acids.

† In these I give a summary of my own experiments. It would be tedious to give the details of each. See also Leyden. (*Beiträge zur Pathologie des Icterus*, Berlin, 1866, p. 57.)

Injections under the skin of the rabbit. Leyden found that rabbits died without fail in 2 or 3 days after the injection of 6 C.C. of a 10 *per cent.* solution under the skin. Immediately after the injection there was excitement, just as with frogs, which also soon disappeared. On the first day, the rabbits took their food; on the second, not; and they became listless. Death sometimes took place in the midst of convulsions. Bile acids were found in the urine by using Hoppe's method, but not bile pigment.*

Injection into the Stomach. Both Röhrig† and Leyden‡ have injected as much as one or two grammes of the soda salts of the bile acids into the stomach of rabbits. Röhrig noted no symptoms, while Leyden observed a diarrhœa to be set up, which apparently killed the animal on the 7th day after the injection. No bile acids or bile pigments were found in the urine. No morbid appearances were found after death.

Injection into the bowels. Röhrig noted that a slow pulse or death invariably took place after the injection of cholalate of soda, and he thinks that the bile acids act as rapidly after injection into the rectum as into the blood vessels.§ This is a matter of some interest in the physiology of the bile.

Leyden injected several C.C. of 10 *per cent.* solution of bile acids into the rectum of two rabbits. Diarrhœa came on in both cases, and in one opisthotonos. Bile acids were recognised in the urine of both.||

A curious symptom was noted by von Dusch,¶ Kühne,** and Feltz and Ritter,†† and others during the

* Leyden, *op. cit.* p. 66.

† Röhrig, *Arch. d. Heilkunde*, 1863, p. 414.

‡ Leyden, *op. cit.* p. 68. § Röhrig, *loc. cit.* || Leyden, *op. cit.* p. 67.

¶ Th. von Dusch, *Untersuchungen und Experimente als Beiträg zur Pathogenese des Icterus*, Leipzig, 1854, p. 20.

** Kühne, *Arch. f. path. Anat.* 1858, Bd. xiv. p. 324.

†† Feltz and Ritter, *Journal de l'Anatomie et de la Physiologie*, 1874, t. x. p. 576 *et seqq.*

injection of the acids into the vein ; the creature thrusts out its tongue and licks its lips as if to free itself from some disagreeable taste. I have noted this appearance myself repeatedly. It is possible it may be due to the presence of the bitter bile acid salts in the blood.

Feltz and Ritter have also remarked an exaggeration of all the secretions, ptyalism, increased secretion of the mucus of the nose, abundance of urine, and loose stools. They look upon these symptoms as an effort of the œconomy to eject the poison. This is quite a possible explanation ; but salivation and purging are so often seen in dogs after any drug that they can hardly be regarded as peculiarities of the action of the bile acids. Mr. Graham Brown noticed no salivation nor vomiting, and no diarrhœa, unless the dose were large, in rabbits under whose skin the bile acid salts had been injected.*

On the Red Blood Corpuscles. It is commonly said by the Germans that Hünefeld was the first to note that bile dissolved the corpuscles.† I have found, however, that this appearance was seen much earlier. Senac noticed that pus and bile, mixed with blood, lessened the red part of the blood.‡ Portal plainly asserts that in experiments of his own he had seen that the bile mixed with blood dissolved the red globules.§

Hünefeld found that the blood, as soon as mixed with bile, became clear, and that the blood-corpuscles disappeared in a moment. The bile of man, oxen, dogs, pigs, cats, rabbits, hens, toads, frogs, and fish, had the same action upon the blood of men, pigs, and frogs ;

* Graham Brown, *Proceedings of the Royal Society of Edinburgh*, 1875, Vol. viii. p. 527.

† Hünefeld, *Der Chemismus in der thierischen Organisation*, Leipzig, 1840, p. 49.

‡ Senac, quoted by Portal, *Obs. sur la nature et le traitement des mal. du foie*, Paris, 1813, p. 156.

§ Portal, *op. cit.* p. 134, note. He quotes from his *Mémoires*, t. ii. p. 279, but I have not been able to verify this reference.

only the nuclei of the frog's blood corpuscles remained for a time unchanged, and then broke up into granules which at last disappeared. The bile of a still-born infant, which was free from bitterness, had none of this property. That of a man who died of a diabetes, very little.

On the other hand, Henle says that ox-bile is the best thing in the world in which to keep the red corpuscles of frogs; and remarks that Hünefeld has not taken note of the concentration of the bile.* Frerichs, too, says that the contents of the gall-bladder dissolve the red corpuscles less readily than does distilled water.† He is inclined, however, to admit that the salts of the bile acids may possess the property of dissolving the red corpuscles.

But most observers support the original statements of Hünefeld. The latest experiments on this matter, those of Koloman Müller, confirm them. Equal parts of filtered bile and blood were mixed, and though the decrease of the red corpuscles could not in all cases be at once detected, yet after a certain time, say an hour, it could always be noted, and in the end not a single corpuscle could be found.‡

After the discovery of the composition of the bile acids by Strecker, Theodor von Dusch was, as far as I can make out, the first to show that the solvent power of the bile upon the red corpuscles was due to the presence of the bile acids in this humour. Two or three crystals of glycocholate of soda were placed in a watch-glass with a drop of human blood; after a few minutes a transparent bright-red circle was found around the the crystal, which in 10 minutes had extended all over the fluid; under the microscope, no trace of the red

* Henle, *Allg. Anat.* Leipzig, 1841, p. 430.

† Frerichs, *Klinik d. Leberkrankheiten*, Braunschweig, 1858, Bd. i. p. 100.

‡ Koloman Müller, *Arch. f. exp. Path.* 1873, Bd. i. p. 222.

corpuscles could be found. Taurocholate of soda showed the same property, but in a higher degree. With taurin itself, the blood-corpuscles were not dissolved, and this experiment has been confirmed by Koloman Müller.* Cholalate of soda gave the same appearances as glycocholate of soda.†

Kühne went a step farther, and examined the blood-corpuscles under the microscope at the moment that they were acted upon by the solution of the bile acids. He allowed the blood and the solution to run together under the covering glass. If a single red blood-corpuscle were kept under the microscope, it disappeared completely, without first losing its cupped shape, or increasing in size, or losing its definition.‡ I can fully support this statement of Kühne's as to the sudden and complete extinction of the red corpuscle when it touches the bile acid solution. I can only describe the appearance by saying that at one moment the red corpuscle is seen, and that, at the next, it is no longer there. It disappears without suffering any change in shape or colour. Traube compares it to the melting of snow in warm water;§ a comparison which I do not think good, as snow does not melt so rapidly as the corpuscle. The way in which distilled water or strong salt solution acts is so different that the destruction of the red corpuscle cannot be set down to the changes in the specific gravity of the fluid. In my own experiments I used a solution of bile acids 12 *per cent.* that is twice the strength of that of Kühne.

Kühne confirms the statement of von Dusch, that the salts of cholalic acid have the same action on the red corpuscles, and Kühne also finds that the same is true of cholidic acid.

* Koloman Müller, *op. cit.* p. 224.

† Th. von Dusch, *op. cit.* pp. 13 *et seqq.*

‡ Kühne, *Arch. f. path. Anat.* 1858, Bd. xiv. p. 333.

§ Traube, *Berlin. klin. Wochenschrift*, 1864, p. 86.

The destruction of the red corpuscle is complete, and no membrane can be brought again into view by the action of iodine, or other colouring matter. But Kuehne finds that this is only true of the red corpuscles of mammals and birds. Though the bile of all vertebrates can dissolve the mammalian red corpuscle, yet the bile acids do not act upon the red corpuscle of frogs as they act upon that of mammals.* The disappearance is slower, the corpuscle changes its shape, but at last the whole of it becomes invisible. If, however, water be added, or better, solution of iodine, it becomes evident that the membrane of the corpuscle has not been dissolved for it is brought into view again.

On Leucocytes. Th. von Dusch declares that leucocytes are dissolved by bile,† a statement agreed to by Charcot.‡ An increase of the white corpuscles in the blood of animals poisoned by the bile acids was noted by Leyden§ and Mr. Graham Brown.||

On the Gases of the Blood. Feltz and Ritter found a slight decrease in the amount of oxygen contained in the blood of a dog poisoned by the bile acid salts, together with a slight increase in the amount of carbonic acid and nitrogen; and they found that blood which contained one and two *per cent.* of glycocholate of soda took up less oxygen and held more carbonic acid than blood which was free from glycocholates.¶ The increase and decrease are, however, so small that they seem to me quite within the bounds of errors of estimation.

* F. Simon (*Animal Chemistry*, Day's translation, London, 1845, vol. i. p. 106.) had noticed that the corpuscles of the frog were not very soluble in bile.

† Th. von Dusch, *op. cit.* p. 15.

‡ Charcot, *Leçons sur les maladies du foie*, Paris, 1877, p. 75.

§ Leyden, *op. cit.* p. 67.

|| J. Graham Brown, *Proceedings of the Royal Society of Edinburgh*, 1875, Vol. viii. p. 520.

¶ Feltz and Ritter, *Journal de l'Anatomie et de la Physiologie*, 1874, t. x. p. 587.

On the Liver Cells. Th. von Dusch first paid attention to the action of bile upon the liver cells. He came to the conclusion that bile, especially if concentrated, made the liver cells transparent and pale, and at last reduced them to a finely granular detritus.* But Kühne has shown that this solution of the cells is only apparent. Under the microscope it is true that the outline of the cell is lost, while apparently the contents are set free. But the contents do not separate from one another; and if the preparation be washed with water, the outline of the cells returns. In my own observations made in 1873, with the livers of freshly killed, healthy mammals, the bile taken from the gall bladder was added to the cells floating in saline solution, and the same appearances as those described by Kühne were seen. The cells lost their shape; they became rhomboidal, pale, and it was hard to make out the nucleus. The outline of the cell became altogether indistinct. Thus far the experiment seemed in favour of von Dusch's views. But the contents of the cells never became free. If made to move, they floated away and preserved the same relation to one another. Further, if acted on by iodine, the outline of the cell again came into view. Like changes in the cells were seen with a 12 per cent. solution of the bile acids.

Robin is also of opinion that the bile does not dissolve the liver cells.†

On the other hand, Kühne believes that this only holds good of the liver cells of mammals and birds. In the livers of frogs, taken in the spring, it could be seen that the outline became pale; and then, that the contents of the cell, which were made up of pigment and fine colourless granules, suddenly burst out, and followed the course of the stream. It is thus a very curious

* Th. von Dusch, *op. cit.* p. 36.

† Robin, *Leçons sur les humeurs*, Paris, 1867, p. 539.

and noteworthy fact that the cells of the liver of the frog should dissolve in bile, while the red corpuscles resist.*

On the glands and muscles. Like many other poisons, the bile acids cause a parenchymatous degeneration of the glands and muscles. Leyden† found this result in very many of the frogs, under whose skin 1. C.C. of a 10 *per cent.* solution of the bile acids had been injected. But it was not seen in all. I can testify to the accuracy of Leyden's observations on frogs, but I have not been able to see the same appearance in rabbits, probably owing to the short time that the poison was allowed to act, as Leyden found changes in two rabbits on whom the bile acids had been allowed to act at least twelve hours, but not in a third. Parenchymatous changes were also seen in dogs. Feltz and Ritter, too, found like changes in the liver and kidneys of dogs,‡ Mr. Graham Brown in those of rabbits,§ and Kemarsky in both of these animals.||

On striped muscles. As early as 1852, Budge made some experiments on this matter, and found that if frog's bile be laid upon the muscles of the frog's thigh, there followed a rapid contraction of the muscle; if the muscle had been cut into beforehand, there was a very marked contraction as a consequence of the irritation.¶ Kühne also stated that bile acted as a marked excitant of muscles, whether applied to the nerves or direct to the muscles; and that the difference of observations was due to the varying degrees of concentration in the bile itself.**

* Kühne, *op. cit.* p. 335.

† Leyden, *Beiträge zur Pathologie des Icterus*, Berlin, 1866, p. 60.

‡ Feltz and Ritter, *Journal de l'Anatomie et de la Physiologie*, 1874, t. x. p. 575.

§ J. Graham Browne, *Proceedings of the Royal Society of Edinburgh*, 1875, Vol. viii. p. 531.

|| Kemarsky, Hofmann and Schwalbe's *Jahresberichte f.* 1875, p. 172.

¶ Budge, *Froriep's Tagesber.* 1852, No. 475, p. 343.

** Kühne, *Arch. f. Anat. Phys. u.s.w.* 1859, p. 235.

Leyden found that, if the muscle of a frog be touched with a solution of bile acids, small fibrillary contractions are seen. If a strong solution be used, the spot touched becomes whitish and opaque, and the whole muscle somewhat contracted.*

The observations of Albers† on the muscles and nerves may be here passed by, as they are general experiments and prove nothing directly as to the muscles.

Johannes Ranke injected a 1 *per cent.* or a .5 *per cent.* of solution of glycocholate of soda into the hind limbs of frogs, and found that the muscles became as hard as wood, and no longer gave tracings when acted on by electricity. On passing saline solution through the vessels of the limb, the muscles became much swollen and transparent. He concludes that the bile acids have a direct paralysing action on muscles; not a weakening action like carbonic acid. The swelling of the muscle after the injection of the saline solution, and failure of the washing out of the muscle to restore its function show that the muscle is changed in its chemical composition.‡

In this last sentence I quite agree with Ranke, and I believe that all the phænomena described by him and by Budge and Leyden may be explained on chemical grounds. In repeating Ranke's experiments, I noticed all the phænomena which he has described. There were the irregular contractions of the muscles of the limbs as the injection passed into them, rigidity and hardness immediately after the injection, and an absence of contraction on the application of electricity to

* Leyden, *op. cit.* p. 97.

† J. F. H. Albers, *Arch. f. path. Anat.* 1862, Bd. xxiii. p. 582.

‡ Johannes Ranke, *Arch. f. Anat. Phys. u.s.w.* 1864, p. 340; also *Tetanus*, Leipzig, 1865, p. 395. After injecting bile acids into the femoral artery of a dog towards the periphery, Leyden found the corresponding muscles stiff and hard to the touch, while the animal could not use the limb. After death on the third day, the muscular fibres showed a well-marked granular change. (*Beiträge zur Pathologie des Icterus*, Berlin, 1866, p. 82).

the sciatic nerves. Knowing, however, that bile acids will coagulate albumen, as a 1 *per cent.* solution will cause turbidity in white of egg, it would seem that the appearances described by Ranke would be very fully explained by the chemical action of the bile acids upon the albuminous bodies of the muscle.

I was thus led to make a series of experiments in which the bile acids should not be immediately injected into the muscle, but should act by the natural process of absorption. The solution of the bile acids was injected into the lymphatic sac, or under the skin of frogs. The amount given varied from .05 to .3 gm. Twelve experiments were made; and in nearly all no change in the curve traced by the myograph could be detected after the injection of the bile acids, the observations beginning immediately after the injection of the bile acids, and lasting up to the time that the muscles would respond to any amount of electricity that I was able to bring to bear upon them.

The method used was as follows: the sciatic nerve was prepared, carefully avoiding all injury of blood-vessels; the tendon of the gastrocnemius was attached to a string, and separated from the heel. The frog was then put into a moist chamber, and the string attached to the *tendo Achillis* fastened to a telegraph lever writing on a revolving cylinder. The sciatic nerve was then irritated by means of electricity from a Du Bois-Reymond's coil; it was applied not oftener than once every minute, and only of such amount as to cause the muscle to contract. In the first two or three experiments the injection was given before the muscle was ready.

As samples of the others I detail two of these experiments.

Jan. 22nd. Excellent normal curves obtained. .1 gm. of bile acids injected under skin of back. No change in

the curves save that they grow smaller in height from 15 to 60 minutes after injection.

Feb. 2nd. .3 grm. of bile acids injected under skin of back. No change in the normal curves from 19 to 92 minutes after injection.

Upon the heart. It has long been known that in some cases of jaundice the pulse becomes slow. But Röhrig deserves the credit of having been the first to point out that it was the action of the bile acids which caused the slow pulse; and that it was not the bile pigments or cholestearin.

He found that if a quantity not less than 2 C.C. of filtered ox bile were injected into the jugular vein of rabbits, a distinct decrease in the number of the heart beats, 7 or 8 in the 15 seconds, could be made out with the stethoscope. An injection of 6 C.C. of bile would bring down the pulse of rabbits to 27 or 30 beats: and by repeated doses, only 12 or 13 beats would be heard in two minutes, and death take place, due as Röhrig states to paralysis of the heart.

Röhrig found that the pigments and the cholestearin had no action on the pulse; neither had taurin nor glycoll; the soda salts of glycocholic and taurocholic acid, on the other hand, had the same action as the bile had itself, and the soda salts of cholalic acid were still more active. It is thus seen that the active elements in the bile are the conjugate acids; and that it is the cholalic acid, not the basic glycoll, nor the taurin, that is the agent of the slow pulse.

Röhrig further found that the slow pulse appeared when the *vagi* had been cut, and also that the frog's heart, when cut out and plunged in a solution of bile acids, beat a fewer number of times than when cut out and plunged in serum, or distilled water; and from these *data* he concluded that it was the ganglia of the

heart and not the *vagi* that were acted on by the biliary acids.*

Landois asserts that the first action of the bile acids is to increase the number of the heart beats. It is true that many poisons have at first the action contrary to that for which they are best known. Landois used only very dilute solutions, such as 10 C.C. of a 2 *per cent.* solution of bile acids diluted with 90 C.C. of distilled water. He found that in frogs, rabbits, and cats, the first result of the injection of the bile or bile acids into the heart was an increase in the number of beats.†

Leyden noticed also in the cut-out heart of the frog an increase of the beats from 11 to 15, and even to 24 in the quarter minute.‡ In my own experiments on the frog, I invariably noticed a slight rise, from 9 in the quarter minute to 10 or 11, and these experiments were made, without disturbing the heart, by the injection of bile acid solution under the skin.

Traube, however, considered that Landois was altogether wrong in saying that small doses of the bile acids increase the beats of the pulse, while large ones decrease them. The difference depends upon the state of the regulating system, whether it be in greater or less activity. If this system be active, there is seen after injection of the bile acids a lowering of the blood pressure with a considerable rise in the number of the pulse. If the activity of the spinal part of the regulating system be removed, then there is a decrease in the beats of the pulse. The bile acids when injected into the jugular vein at once meet with and destroy, or injure, a certain number of red corpuscles; then the

* Röhrig, *Arch. der Heilkunde*, 1863, p. 385. There is also an Inaugural Dissertation, *Ueber den Einfluss der Galle auf der Herzthätigkeit*, Leipzig, 1863, which I have not been able to see.

† Landois, *Deutsche Klinik*, 1863, p. 449.

‡ Leyden, *op. cit.* p. 93.

blood containing these dissolved red corpuscles and the bile acids is quickly carried through the right side of the heart into the lungs. The red corpuscles being dissolved can no longer act as the carriers of oxygen, and the blood is brought by the pulmonary veins to the left side of the heart and distributed to the coronary arteries; this blood is incapable of exchanging oxygen with the muscular walls of the heart, and they are therefore injured, and in this way a slow pulse is seen.*

About the same time Johannes Ranke arrived at the conclusion, somewhat similar to that of Traube, that the bile acids have a paralysing influence upon striped muscular tissue. To the influence of the bile acids upon the muscular fibres of the heart the slow pulse is therefore due.†

The statements as to the cause of the slow pulse being thus so contradictory, I attempted a few years ago a research upon this subject, the results of which were laid before the Royal Society.‡ The first element which it was necessary to eliminate was the influence of the *vagus*; and thanks to von Bezold's discovery, a ready means in atropine was at hand, by which the inhibitory function could be removed.

The heart of the frog lends itself very readily to all researches of this kind; if arranged in a Bowditch's apparatus, the circulation can be readily kept up for hours, if fed by serum; and if the aorta be connected with a manometer, the number and force of the pulsations of the heart can be easily registered.

* Traube, *Berlin. klin. Wochenschrift*, 1864, p. 86, and *Gesammelte Beiträge*, Berlin, 1871, Bd. i. p. 366.

† Johannes Ranke, *Arch. f. Anat. Phys. u.s.w.* 1864, p. 340: also in *Tetanus*, Leipzig, 1865, p. 395. See his experiments above, p. 199.

‡ Wickham Legg, *Proceedings of the Royal Society of London*, 1876, Vol. xxiv. p. 442.

FIG. 1.

Normal tracing
of frog's heart.

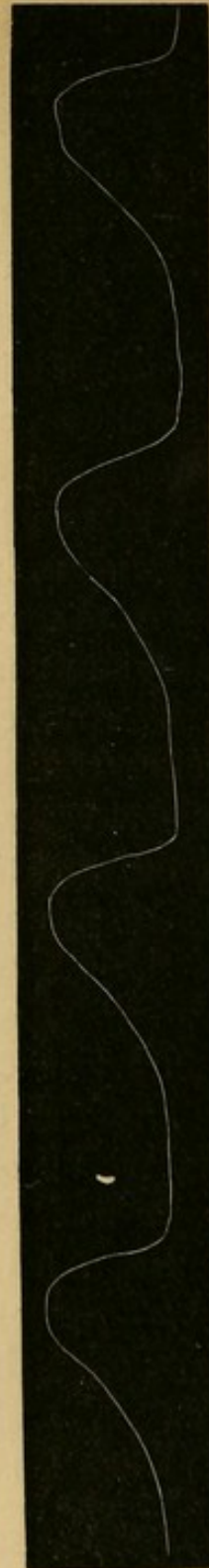
FIG. 2.

Tracing under influence
of atropine.

FIG. 3.

First effect of the bile
acid salts.

FIG. 4.



Later effect of the bile
acid salts.
(The cylinder having
been reversed, the trac-
ing must be read in a
direction opposite to the
other three).

FROG'S HEART IN BOWDITCH'S APPARATUS.

Time in Seconds.	Number of Pulsations.	Height of Curve in millimeters.	Remarks.
130	31	5.5	See Fig 1.
"	32	6	
"	38	4	Curves double topped.
"	31	6	Atropia introduced into the serum, so that it contained .028 per cent. (See Fig. 2.)
120	24	7	Bile acids introduced into the serum.
"	16	7	Records in continuous 30 seconds. (See Fig. 3.)
"	16	8	Pulse now goes in pairs, 6.5 seconds between each pair of pulsations: between the pulses of each pair 3.2 seconds.
"	16	8.5	These do not go in pairs.
"	16	9	
"	16	8	These go in pairs.
130	13	12	A great change in character of curves. Systole reaches <i>maximum</i> height in 1.5 seconds. They slowly sink, scarcely meeting abscissa until the next contraction begin. They are nearly all alike. One takes up 23 mm. others 38 mm. (See Fig. 4.)
"	12.5	10	Immediately after the heart ceases to beat. No contractions upon electrical irritation.

Four other like experiments, with a like result, were made in December, 1872, and January, 1873. In one of them the bile acids were added to the serum first and the atropine added afterwards; but the same results were attained. The slowness of the pulse arose as before, and was unchanged by the addition of the atropine.

Another series of experiments on the irritability of the *vagus* was made.

The heart and right *vagus* of a frog laid bare, the heart beating 12 in 15 seconds. The *vagus* was then irritated by induced electricity and the heart stood still in diastole. Three or four drops of the solution of atropia of the British Pharmacopœia were now let fall upon the heart. After five minutes the beats were 7 in 15 seconds. The right *vagus* was then again irritated by induced electricity with no change in the heart. After 10 minutes, four drops of a 10 per cent. solution of bile acids were let fall upon the heart and neighbourhood. Thereupon, for nearly a minute, the heart beats

rose to 10 in 15 seconds, but directly after fell to 6 in 15 seconds, the right *vagus* was again irritated but no change followed. Three minutes after, the beats were 5 in 15 seconds. The experiment was then broken off.

Two other experiments were made with like results. They would seem to show that the bile acids do not restore to the *vagus* the inhibitory power destroyed by the atropia.

With mammals I have attained like results.

If the inhibitory action of the *vagus* can therefore be excluded, there remain two other factors as a cause of the slow pulse, the muscular walls and the ganglia of the heart.

To deal first with the muscular walls, to the failure of which both Traube and Johannes Ranke attribute the slow pulse.

It has already been shown (p. 198.) that the bile acids have no physiological action upon striped muscular tissue, although they have a marked chemical action when injected into muscles. Have they, then, any chemical influence upon the ventricle? To test this supposition, I thought of making some experiments upon the action of the bile acids on the ventricle when separated from the rest of the heart.

It is commonly said that the ventricle of the frog's heart continues to beat for some time after it be severed from the auricles. I found, however, that the time was not long enough, nor the beating of the ventricle constant enough, to enable me to judge of the difference in time taken to bring the ventricle to a standstill if immersed in serum, or in serum containing 1 *per cent.* of bile acids. I fell back therefore on a method employed by Luciani* in Ludwig's Laboratory. It consists in introducing into the ventricle of the frog's heart, a tube divided vertically by a septum, and tying the ventricle on to the

* Luciani, *Arbeiten aus dem phys. Anstalt zu Leipzig*, 1873, Jahrg. vii. p. 120.

cannula below the auricles. The heart is supplied by serum through the double cannula and each pulsation is recorded by a manometer. I made five of these experiments, but I could detect no change in the alternate periods of rest and of contractions, as described by Luciani, after the introduction of bile acids in 1 *per cent.* into the serum, nor after the removal of the bile acid serum and the feeding of the heart with pure serum. Both before and after the use of the bile acids the contractions of the ventricle were alike. It would seem, therefore, that the bile acids have no action, either chemical or physiological, upon the ventricle of the frog's heart separated from the auricles.

If, then, the bile acids have no influence upon the ends of the *vagus* in the heart, nor upon the muscular tissue, there remains, in the present state of knowledge, only one other cause of the heart's movement which may beget a slow pulse; the ganglia of the heart. How these are affected by the bile acids there is no direct evidence to show. I do not know of any means by which these ganglia can be put out of play; and thus immediate proof that the ganglia are concerned is wanting. But if an argument, *per viam exclusionis*, be allowed, then it must be that the slow pulse is due to the action of the bile acids upon the cardiac ganglia.

I only became acquainted with the observations of J. Steiner a few months ago. He finds, as I do, that the slow pulse is not due to the excitement of the ends of the *vagus*, as the slow pulse appears after atropia has been given. But he has also made an observation of much interest. If bile be let fall upon the back surface of the frog's heart, there is at once a fall in the pulse, or even complete cessation of the heart's beats. But if the bile only touch the fore surface of the heart there is no change in the pulse for 10 minutes. Further, if the ventricle were cut off after Stannius' ligature were

applied, the sinus still beat; but if touched with bile, the sinus at once ceased to pulsate. Again, if the Stannius' ligature were applied to the heart, the sinus taken away and the ventricle cut off, the auricle still beat, and continued to beat after it was touched with bile, though after some time the number of pulsations became less.

Steiner thinks that it is proved that the bile acts upon only one of the ganglia of the heart, that in the sinus, and not on the atrio-ventricular ganglia.*

On the hearts of snails. It has been asserted that the heart of the snail shows no nervous elements. I have made a number of experiments on the action of the bile acids upon the heart of this animal, but I have perceived no change worthy of note. The bile acids seemed to have no influence, neither increasing nor decreasing the number of pulsations, which are always very irregular.

On the lymphatic hearts of frogs. Röhrig has made some observations on the influence of the bile acids on the lymphatic hearts of the frog. Both hearts were laid bare, and six drops of a 5 *per cent.* solution of glycocholate of soda spread upon the muscular tissue. Before the bile acids, the number of beats was 12 in 15 seconds; one hour after, 10 beats; two hours, 8; three hours, 6; four hours, 4. At the end of four hours the least number of beats was attained, and at the end of six, the usual number was again seen.

Röhrig thinks that the action of the bile acids upon the lymph heart runs parallel with that upon the blood heart; though with small doses the lymphatic hearts may cease to act after a few hours, while the systemic heart is still beating, and the frog shows no change.†

My own observations lead to a conclusion altogether

* J. Steiner, *Arch. f. Anat. Phys. u.s.w.* 1874, p. 474.

† Röhrig, *Arch. d. Heilkunde*, 1863, p. 418.

different from that of Röhrig. And perhaps I may be allowed to say that I somewhat regret my own results, as, if the bile acids had shown a distinct action on the lymphatic heart, it would have been an important aid to the proof that the cause of the slow pulse is nervous. I made six observations, and in no case found the rate of the pulsation of the lymphatic hearts changed soon after the administration of the bile acids by subcutaneous injection. The lymphatic heart only began to beat more slowly when general death was setting in from the action of the poison. The systemic heart, on the contrary, shows the action of the poison within a few minutes of its injection, and the pulsations may sink from 13 to 3 in the 15 seconds in seven minutes after the injection of 1 C.C. of a 10 *per cent.* solution of bile acid under the skin.

I give the details of one experiment. On Dec. 24th. the right posterior lymphatic heart was exposed at 10.55 a.m. The pulsations vary from 7 to 9 in 15 seconds. At 11.5 the average is 9 in 15 seconds. At 11.5 one C.C. of a 10 *per cent.* of bile acids was injected under the skin of the neck.

11.12 a.m.	10 in 15 seconds.	12.20 p.m.	another injection.
11.15 "	9 "	12.25 "	11 in 15 seconds.
11.20 "	9 "	12.31 "	10 " "
11.24 "	struggles.	Lymphatic heart now ceased	
11.28 "	9 "	to act.	
12 noon	10 "	2 p.m. animal found dead.	

On the blood-pressure. Traube first called attention to the action of the bile acids on the blood-pressure. He found that if an animal be rendered motionless with woorara, and a bile acid soda salt be injected into the jugular vein, not towards the heart, but towards the head, the blood-pressure is much decreased and the pulse increased in frequency. If the dose of woorara have been large, the same results are obtained as those

seen after division of the *vagi*: great decrease in the number of the pulse and in the blood-pressure. In both cases, however, there follows either an increase or a decrease of the frequency of the pulse; and, at the same time, a rise in the blood-pressure.

There is a great difference, too, according to the vessel into which the injection is made. An injection into the carotid will completely remove the effects of an injection into the jugular. For example, if the *vagi* be divided, and the bile acid salts injected into the jugular vein, there is a lowering of the blood-pressure and a decrease in number of the pulse. If, while the pulse and the pressure are sinking, another dose be injected into the carotid, the pulse and pressure at once begin to rise. If a similar experiment be made while the *vagi* are undivided, there are seen, after injection into the vein, lowering of the blood-pressure and increase in the number of the pulse; if, while these phænomena are still showing themselves, an injection be made into the carotid, there is increase of the blood-pressure and lowering of the pulse.*

Kemarsky found that, with animals under the influence of woorara, there was a fall in the blood-pressure. This fall is caused solely by the action of the bile acids on the heart, as if both *vagi* and spinal chord be divided the fall is still seen. If the *vagi* be not divided there is an increase in the number of the heart beats; if divided, the pulse becomes slow, so that Kemarsky thinks the slow pulse due to the action of the *vagus*.†

I have myself made some observations with the kymograph on the blood-pressure as affected by the injection of the bile acid salts into the blood; but in some re-

* Traube, *Berlin. klin. Wochenschrift*, 1864, pp. 86 and 147. Also in his *Gesammelte Beiträge*, Berlin, 1871, Bd. i. p. 366.

† Kemarsky, *Jahresberichte ueber die Fortschritte d. Anat. u. Phys. f.* 1875, Bd. iv. p. 171. Reasons for not accepting this conclusion of Kemarsky as to the *vagi* have been given above. (p. 205.)

spects I have not attained the same results as those of Traube.

April 30th. A middle-sized rabbit, kymograph in connexion with the carotid artery.

TIME	PULSE IN 15 SECONDS	BLOOD-PRESSURE IN MILLIMETERS
Normals	{ 67	110
	{ 70	126
	{ 72	116
12. 59' 50" p.m. Injection of 1 C.C. of a 12 <i>per cent.</i> solution of Platner's crystallised bile into the external jugular vein towards the heart.		
1. 0' 11". Injection ended. From 12. 59' 50" to 12. 59' 58" there were 40 beats of the heart; from this time to 1. 0' 11" there were 52 pulsations, and the blood-pressure began to fall immediately.	71	108
1. 0' 19" .6	65	78
1. 0' 34" .6	61	84
1. 1'	58	90
1. 3'	62	94
	68	106

In this experiment it will be seen that an injection of the bile acid salts into the jugular vein towards the heart was quickly followed by a fall both in the blood-pressure and the number of the pulse, though according to Traube there should be a fall in the pressure and an increase in the pulse.

In another experiment on a rabbit the only effect noted was an elevation of the blood-pressure slight and rapidly passing away.

April 28th. Black rabbit, large. Kymograph in connexion with carotid artery. Pulse not counted.

TIME	BLOOD-PRESSURE IN MILLIMETERS
3. 25'	92
3. 28'	98

TIME		BLOOD-PRESSURE IN MILLIMETERS
3. 29' 15"	Injection of 1 C.C. of a 10 <i>per cent.</i> solution of Platner's crystallized bile into the right external jugular towards heart.	98
3. 29' 45"	Injection over	96
3. 20' 55"		104
3. 30'		98
3. 30' 45"		100
3. 32'		100
3. 33'		104
3. 34'		106

A clot now formed and the artery ceased to record.

In all the other experiments which I have made I have noticed a fall in the blood-pressure after the injection of the bile acid salts into the jugular vein. I have been somewhat surprised at the little effect which one, two, and three C.C. of a ten *per cent.* solution of bile acid salts, have when injected into the jugular. On the other hand, the same dose injected into the carotid causes at once marked symptoms, with a considerable rise in the blood-pressure. The blood-pressure sinks during the injection, but at once begins to rise somewhat irregularly and keeps high for a few seconds. It then falls, and comes to an end with the death of the rabbit.

The peculiar symptoms seen on injection into the carotid are described immediately below.

On the Respiration. A very curious appearance after the injection of the bile acids into the carotid was first noticed by Traube; a spasm of the respiratory muscles takes place, and the diaphragm is held in deep inspiration. Apnœa follows, but the heart still beats. If artificial respiration be practised, the animal can be kept alive. If only small doses be given, there is a great fall in the number of respirations, even to 2 in a minute.* Leyden has repeated these experiments.†

* Traube, *Berlin. klin. Wochenschrift*, 1864, p. 147. Also in *Gesamm. Beiträge*, Berlin, 1871, Bd. i. p. 378.

† Leyden, *Beiträge zur Pathologie des Icterus*, Berlin, 1866, p. 70.

The inspiratory spasm is very well marked, as I can testify from my own observations; and it persists in the rabbit even after the removal of all the cerebrum above the tentorium, except the *corpora quadrigemina*. After their removal, the spasm is no longer well marked.

Mr. Graham Brown found that the respirations of rabbits were perceptibly decreased in rapidity after the injection of the bile acids under the skin.* Albers noted, 20 minutes after pure glycocholic acid had been placed under the skin of frogs, that the breathing was quicker; later on dyspnœa.†

On the Nervous System. It has already been noted that epileptiform convulsions, and tetanus have followed the injection of bile, even if filtered, into the veins. The same phænomena have followed the injection of the pure bile acid salts. It is thus probable that the bile acids in the filtered bile are the active agents in causing the nervous symptoms.

Theodor von Dusch noted these tetanic symptoms and opisthotonos, followed by sudden death, after the injection of solutions of glycocholate of soda and of taurocholate of soda into the jugular vein. A large amount, 8 and 16 C.C. of a 20 *per cent.* solution of glycocholate of soda, could be injected into the *vena saphena* of a dog without causing more than passing symptoms. After death, the lungs were found full of hæmorrhages, the right side of the heart filled with clotted blood; the left empty; while the *vena cava inferior* was distended with blood.‡ Similar observations, though less minutely detailed, have been recorded by nearly every other observer who has experimented with the bile

* J. Graham Brown, *Proceedings of the Royal Society of Edinburgh*, 1875, vol. viii. p. 527.

† J. F. H. Albers, *Arch. f. path. Anat.* 1862, Bd. xxiii. p. 582.

‡ Th. von Dusch, *Untersuchungen und Experimente also Beitrag zur Pathogenese des Icterus*, Leipzig, 1854, pp. 18 *et seqq.*

acids, such as Frerichs,* Kühne,† Leyden,‡ Feltz and Ritter.§

At the time at which Theodor von Dusch wrote, the doctrine of thrombosis of the pulmonary artery was less widely spread than at present, and it is hardly surprising that he failed to draw the conclusions, which now seem to lie on the surface. Johannes Ranke and Baldauf, indeed, apparently without being acquainted with Theodor von Dusch's observations, have come to the conclusion that the sudden death is due to thrombosis of the pulmonary artery.|| The blueness of the lips, the tetanic convulsions, the expulsion of the urine and fæces, after death the distension of the right side of the heart and the vessels leading into it, the right side being sometimes filled with clots,¶ the pulmonary hæmorrhages, and the emptiness of the arteries, all noted by von Dusch, make the case a typical one of death from pulmonary embolism. The explanation which Johannes Ranke gives of the formation of the thrombosis is very probable. The bile acids dissolve the red corpuscles; as a consequence of the solution of the red corpuscles, a clot immediately forms, which is carried to the heart or into the pulmonary artery. And this explains the fact noted by Th. von Dusch that when the injection was made into a vein at a distance from the heart, such as the crural or saphena, sudden death did not always take place.** Johannes Ranke found after the same experiment that the vena cava, as high as the liver, was filled with a thrombus, while many of

* Frerichs, *Klinik d. Leberkrankheiten*, Braunschweig, 1858, Bd. i. p. 404.

† Kühne, *Arch. f. path. Anat.* 1858, Bd. xiv. p. 326.

‡ Leyden, *op. cit.* p. 72.

§ Feltz and Ritter, *Journal de l'Anatomie et de la physiologie*, 1874, t. x. p. 571.

|| Johannes Ranke, *Die Blutvertheilung und der Thätigkeitswechsel der Organe*, Leipzig, 1871, p. 164.

¶ Th. von Dusch says that he found a thrombus in a large pulmonary vein (p. 21). This is probably an error of observation for pulmonary artery.

** See the older observations with this same result, p. 118.

the smaller branches of the pulmonary artery were also filled with clots.

Johannes Ranke states that the dose of the bile, or the bile acid salts, which is enough to cause death in rabbits, is only fifteen milligrammes. I do not think that this is always the case. I have injected 50, 200, and even 800 milligrammes of Platner's crystallized bile in 10 *per cent.* solution into the jugular veins of rabbits, in different individuals, without causing thrombosis of the pulmonary artery or of the right heart. No obvious effect was caused by the injection of 50 or 200 milligrammes. But after the dose of 800 milligrammes, the pulse and respiration at once fell, and the rabbit appeared to be dying; it was killed at once by opening the chest; the heart was found still feebly contracting on the right ventricle and auricle; but none on the left side. Irritation of the ventricles with Pulvermacher's forceps called forth no contractions; but the same irritation to the phrenic nerve caused violent contractions of the diaphragm. Direct irritation of the muscles of the thigh, and of the anterior crural nerve was followed by marked contractions. Heart and pulmonary artery followed with a fine pair of scissors, but no clots were found. Urine from the bladder was turbid and straw-coloured, but showed no reaction with nitric acid.

Probably the difference in observation is due to a difference in the food of the animals; and the difference between the older experiments spoken of above, must be explained on the same grounds, or a difference in the constitution of the blood.

Huppert injected 3.3 grm. of glycocholate of soda, dissolved in 20 C.C. of water, into the jugular vein of a dog, and found that the creature, up to that moment very restless, became quiet, and fell into a sleep from which he could hardly be aroused.* In the same way,

* H. Huppert, *Arch. d. Heilkunde*, 1864, p. 241.

Mr. Graham Brown noticed much drowsiness, ending at last in coma, after the injection of the bile acids under the skin of rabbits. No convulsions were noticed; nor did the pupil show any change.* Albers speaks of convulsions and other nervous symptoms, after pure glycocholic acid had been introduced under the skin of frogs.† Leyden does not think that the bile acid salts are a direct irritant. When the sciatic nerve of a frog with the muscles still attached to it was laid in bile, no contractions of the muscles appeared.‡ I have no doubt of the action of the bile acid salts as narcotics. When moderate doses are given to frogs, the animals shortly become torpid, insensible to all stimulus, showing no reflex action whatever. They lie, with contracted pupils, as if in a deep sleep.

I have made some observations upon the changes in the reflex movements which follow the administration of bile acid salts. Out of five experiments, nearly all alike, I give the details of one.

Dec. 19. The anterior cerebral hemispheres of a frog were removed, the optic thalami being left uninjured. The foot of the frog was irritated by being plunged in water, made just perceptibly acid to taste by sulphuric acid.

The numbers represent the time in seconds which passed between the plunging of the foot into, and its withdrawal from, the water with which it was irritated.

12.22 p.m. 12, 6, 7, 8, 6, 7, 6.

12.32 p.m. .5 C.C. of a 10 *per cent.* solution of bile acids injected under the skin of the back.

12.39 p.m. 1, 2, 1, 1, 29, 27, 15, 16, 21, 28, 22, 26.

1 p.m. The head was cut off.

1.25 p.m. 9, 9, 9, 9, 10, 10, 10.

* J. Graham Brown, *Proceedings of the Royal Society of Edinburgh*, 1875, Vol. viii. p. 530.

† J. F. H. Albers, *Arch. f. path. Anat.* 1862, Bd. xxiii. p. 582.

‡ Leyden, *Beiträge zur Pathologie des Icterus*, Berlin, 1866, p. 95.

In all cases a minute passed between the application of the irritant; and the foot was well washed with distilled water after each observation.

It would appear that the reflex irritability is decreased by the action of the bile acids; a statement in which Kemarsky also joins.*

Upon the serous membranes. It is well known that an escape of bile into the peritonæum is an almost fatal accident, peritonitis being at once set up. This property of the bile would seem to be due to the presence of the bile acid salts, as the same violent peritonitis follows the injection of these salts into the peritonæum.

On the temperature. Röhrig was struck by the coldness of the animals poisoned by the bile acid salts, and found their temperature much lower than natural.† Feltz and Ritter also speak of a low temperature as a result of poisoning by the bile acids.‡ Kemarsky found the temperature to be lowered in direct proportion to the amount of bile acid salts injected into the blood; an inconsiderable rise of temperature preceded the fall.§ Huppert, in two dogs, found very little change;|| the thermometer in the rectum being constant at $37^{\circ} \cdot 6$ C. or $37^{\circ} \cdot 8$ C. ($99^{\circ} \cdot 6$ F. or 100° F.)

Röhrig goes so far as to propose the bile acids as a remedy in fever to bring down the temperature. It is possible, however, that the lowering of the temperature is not due to a specific action of the bile acids, for many poisons cause a fall in the temperature some hours before they put an end to life.

On the Urine. After the injection of the bile acid salts into the blood, the urine quickly becomes high-

* Kemarsky, *Jahresberichte ueber die Fortschritte d. Anat. u. Phys. f.* 1875, Bd. iv. p. 171.

† Röhrig, *Arch. d. Heilkunde*, 1863, p. 394.

‡ Feltz and Ritter, *Journal de l'Anatomie et de la Physiologie*, 1874, t. x. p. 576.

§ Kemarsky, *Jahresberichte ueber die Fortschritte d. Anat. u. Phys. f.* 1875, Bd. iv. p. 171.

|| H. Huppert, *Arch. d. Heilkunde*, 1864, p. 241.

coloured from the presence of hæmoglobin. No red blood corpuscles can be found, but abundance of casts of the urinary tubules, with dark granules. So far all observers are agreed. But Frerichs announced that in the urine is also to be found bile pigment; and he explains the presence of the bile pigment by a metamorphosis in the circulation of the colourless bile acid salts into pigment.* Kühne found bile pigment in the urine after the injection of bile acids into the circulation, but apparently attributed the presence of the pigment to the setting free of hæmoglobin into the plasma.†

I have myself been unable, in numerous experiments, to satisfy myself of the presence of bile pigment in the urine of rabbits after the injection of the bile acids into the blood. I am inclined to believe that the difference in observation is due to the animals experimented upon. The urine of dogs often shows a Gmelin's reaction, when the animals are believed to be in perfect health.

Mr. Graham Brown records the appearance of albumen and bile pigments in the urine of rabbits, as a rare event, after bile acid salts have been injected under the skin.‡

The same observer noted the presence of red blood corpuscles once or twice in the urine; but the spectrum did not show the characteristic absorption bands of blood on the two occasions when the test was applied. This is another instance of the difference in the effect caused, according as the poison is injected into the blood, or under the skin.

Mr. Graham Brown found in nearly every case a great rise in the amount of nitrogen excreted by the

* Frerichs, *Klinik d. Leberkrankheiten*, Braunschweig, 1858, Bd. i. p. 404. See also *Arch. f. Anat. u. Phys.* 1856, p. 59, note.

† Kühne, *Arch. f. path. Anat.* 1858, Bd. xiv. p. 324. See also his *Lehrb. d. phys. Chemie*, Leipzig, 1866, p. 89.

‡ Graham Brown, *Proceedings of the Royal Society of Edinburgh*, 1875, Vol. viii. p. 528.

urine immediately after the injection of the bile acid salts under the skin; in one case the amount passed in the first 24 hours after the injection was just double the average of the three foregoing days.

Feltz and Ritter made two observations with the taurocholate of soda, but whether it were injected under the skin of the dog or into the veins does not appear. They noted a slight increase in the amount of nitrogen, but it was so slight that it might be quite within the physiological boundaries; and the urea was markedly decreased and the uric acid increased.* The urine seems in most cases to be alkaline.

PHYSIOLOGICAL ACTION OF THE DERIVATIVES OF THE BILE ACIDS.

Cholalic acid. It was noticed, as early as 1854, by Theodor von Dusch that cholalate of soda dissolved the red corpuscles as readily as the glycocholate,† and Röhrig found that the pulse became more rapidly slow when cholalate of soda was injected into the veins, than when the bile acid salts themselves were used.‡

Hoppe-Seyler, also, saw most severe symptoms follow the injection of two grammes of the same salt into the jugular vein of a dog. The urine, much decreased in quantity, held blood-colouring matter and albumen. There were vomiting and diarrhœa, and in two days the animal was dying. After death many hæmorrhages were found in the intestines which held little else but blood and bile. The kidneys on section looked quite black; and the tubules were filled with blood crystals.§

* Feltz and Ritter, *Journal de l'Anatomie et de la Physiologie*, 1874, t. x. p. 585.

† Th. von Dusch, *Untersuchungen und Experimente als Beitrag zur Pathogenese des Icterus*, Leipzig, 1854, p. 15.

‡ Röhrig, *Arch. d. Heilkunde*, 1863, p. 397.

§ Hoppe-Seyler, *Arch. f. path. Anat.* 1862, Bd. xxv. p. 183.

Feltz and Ritter came to conclusions quite different from those of observers who have gone before them; so different that it would almost appear that they experimented with a body differing in chemical composition. They find cholalate of soda much feebler in its action than the glycocholate and the taurocholate; the doses require to be much larger to produce the same appearances. They have never seen any blood in the urine and only by accident any colouring matters. The blood also does not appear to be changed.*

I should myself feel inclined to put greater trust in the observations of Röhrig and Hoppe-Seyler on the action of cholalic acid, than in those of Feltz and Ritter. For it would be a strange thing if a body which is the foundation of the bile acids, and allied to them in so many chemical and physical properties, should prove as inert, as Feltz and Ritter found it, in its physiological properties.

Choloidic Acid (Demarçay). Feltz and Ritter saw no perceptible changes follow the injection of two grammes of the soda salt of this acid into a dog weighing 5.750 kilogrammes†

Kühne states that the red corpuscle is dissolved by choloidic acid.‡

Dyslysin. This body, dissolved in cholalate of soda, was injected into a dog by Feltz and Ritter in doses of two grammes. No symptoms whatever were noticed.§

Glycocoll. All observers who have made observations with this body have stated that it is harmless to the animal œconomy.|| Schultzen and Nencki found a great increase in the urea, corresponding to the

* Feltz and Ritter, *Journal de l'Anatomie et de la Physiologie*, 1875, t. xi. p. 148.

† Feltz and Ritter, *loc. cit.*

‡ Kühne, *Arch. f. path. Anat.* 1858, Bd. xiv. p. 333.

§ Feltz and Ritter, *loc. cit.*

|| Röhrig, *op. cit.* p. 396. Feltz and Ritter, *op. cit.* p. 151.

amount of nitrogen in the glycocoll, after feeding animals with this body; but it does not appear to have acted in any way as a poison.*

Taurin. Neither is taurin endowed with any very active physiological gifts. Nearly all observers look upon it as inert.† Salkowski, however, found that rabbits were somewhat sensitive to its use, much more so than dogs or men. When given by the mouth, the greater part of the taurin reappears in the urine of rabbits; there is four or five times as much sulphuric acid as natural; and it is to the waste of alkali that Salkowski attributes the injurious action of taurin.‡

PHYSIOLOGICAL ACTION OF THE BILE PIGMENTS.

Röhrig appears to have been the first to make experiments with the bile pigments. He found that saturated solutions, in soap, of cholepyrrhin (bilirubin) and of bilifulvin, injected into the circulation in doses of 6 to 8 C.C. had no influence on the action of the heart.§

Feltz and Ritter found that the bile pigments had no marked action on the animal œconomy. The injection of bilirubin was followed by an obstinate constipation, and an increase in the amount of urine in which bilirubin could be readily detected. The writers note much the same appearances after the injection of biliprasin, bilifuscin, and bilihumin.¶

To sum up, it may be stated that the bile pigments are physiologically inert.

* Schultzen and Nencki, *Zeitschrift f. Biologie*, 1872, Bd. viii, p. 124.

† Th. von Dusch, Röhrig, and Feltz and Ritter, *locis citatis*; Koloman Müller, *Arch. f. exp. Pathologie*, 1873, Bd. i. p. 233.

‡ Salkowski, *Berichte der deutschen Chemischen Gesellschaft zu Berlin*, 1872. Jahrg. v. p. 637. See an abstract by himself of his work in Virchow and Hirsch's *Jahresbericht f.* 1873. Bd. i. p. 159.

§ Röhrig, *op. cit.* p. 400. Cf. p. 86. of this work.

¶ Feltz and Ritter, *op. cit.* p. 154.

PHYSIOLOGICAL ACTION OF CHOLESTEARIN.

Dr. Austin Flint, the younger, first called attention in 1862* and again in a pamphlet published in the French language at Paris in 1868† to the physiological action of cholestearin. He first attempts to prove that this body is an excremental matter formed by the metamorphosis of the brain and excreted by the liver. In the upper part of the intestine, the cholestearin is changed into a body called stercorin. This is then cast out of the body and forms a most important element in the excretions of the body. If the liver do not act properly, if there be suppression of its secretion, then the cholestearin is retained in the blood and acts as a poison. This pathological state Dr. Flint calls cholestearæmia, and to it the nervous symptoms seen in jaundice may be set down.

It may be noted that Dr. Flint made no direct experiments with cholestearin upon animals. His experiments are a series of estimations of the amount of cholestearin in the blood. The trouble and uncertainty which attend all estimations of bodies in the blood are well known; and it has struck me in looking down the figures given by Dr. Flint that in very many cases the amount of cholestearin found varies inversely with the amount of blood submitted to examination. Where a larger amount of blood has been examined, a smaller percentage of cholestearin has been found, and *vice versâ*.

The views of Dr. Flint have not met with universal acceptance; and attempts have been made to test their value by directly injecting cholestearin into the blood. A difficulty, however, arises from the insolubility of cholestearin in the ordinary fluids indifferent

* Austin Flint, jun. *American Journal of the Medical Sciences*, 1862. vol. xliv. p. 305.

† *Recherches exp. sur une nouvelle Fonction du Foie*, Paris, 1868.

to the blood. Koloman Müller made a sort of emulsion by first finely rubbing up the cholestearin with glycerine, and then adding solution of soap. A thick emulsion was thus got in which the cholestearin was very finely divided, 8. C.C. holding 45 milligrammes of cholestearin. This emulsion of cholestearin was injected into the veins of about 9 dogs, and the injection was followed by coma, and death. Koloman Müller concludes that the nervous appearances seen in jaundice are due to the accumulation of cholestearin in the blood.*

It would be worth seeing if the nervous symptoms described by K. Müller follow an injection of the same emulsion under the skin. It seems very likely that a thick emulsion injected into the veins would be followed by severe symptoms, not to be all set down to the physiological action of cholestearin.

On the other side are the experiments of several observers. Pagès, the year after Dr. Austin Flint published his pamphlet in French, made cholestearin the subject of his inaugural thesis. He apparently made his experiments under the direction of Feltz and Ritter. The first experiments were not likely to give any information, as the cholestearin was dissolved in æther, and æther is a fluid to which the blood is by no means indifferent. In the last two experiments he attempted to dissolve the cholestearin in soap. Koloman Müller says that he was unable to obtain a true solution with soap. Be this as it may, 25 milligrammes of cholestearin injected into the veins caused no symptoms whatever. Pagès thinks that whatever symptoms are caused by cholestearin are due to its solid particles acting as emboli.†

* Koloman Müller, *Arch. f. exp. Pathologie*, 1873, Bd. i. p. 213.

† Henri Pagès, *De la cholestérine et de son accumulation dans l'économie*, Thèse de Strasbourg, 1869. These experiments have been republished by Feltz and Ritter, *Journal de l'Anatomie et de la Physiologie*, 1875, Année xi. p. 166.

A Russian observer, M. Chomjakow, chose oil of almonds as a vehicle. A 5 *per cent.* solution in this oil retained its transparency at 37° to 40° C. 7.5 C.C. of the solution, corresponding to 345 milligrammes of cholestearin, were injected into the veins of cats. The following were the results: either the animals underwent the injection without any symptoms at all, or death followed immediately upon the injection either of cholestearin in solution or of almond oil alone. In this case the cause of death was infarction of the pulmonary artery.*

V. von Krusenstern, in O. Liebreich's laboratory at Berlin, came to precisely the same result as Chomjakow, but with a different solvent. With a 3 *per cent.* solution of stearin soap he made a 0.5 *per cent.* solution of cholestearin. The daily injection of this solution (10 to 90 C.C. = 5 to 45 milligrammes of cholestearin), into the veins of dogs caused not the least change in their state.†

Looking upon these experiments and comparing them with those of Koloman Müller, it will be hard to come to any other conclusion than that cholestearin is a harmless body, the injection of which into the veins is followed by no evil results. If this position be granted, the theory of a cholestearæmia must fall.

* M. Chomjakow, *Kriegsmedizinische Zeitschrift* (Russian) 1872. Quoted by V. von Krusenstern, *Arch. f. path. Anat.* 1875, Bd. lxx. p. 412.

† V. von Krusenstern, *op. cit.* p. 418.

CHAPTER X.

THE ETYMOLOGY, HISTORY, AND ÆTIOLOGY OF JAUNDICE.

JAUNDICE signifies a yellowness of the skin. It comes from the French word *jaune*, yellow. The Greeks called the disease *icterus*. Of this word Aretæus says: "it is derived from certain four-footed and terrestrial animals, called *ικτιδες* whose eyes are of this colour."* Pliny the elder, on the other hand, says there is a bird called *icterus*, the sight of which was cure to the jaundiced patient, but death to the bird.† Aretæus is, no doubt, right. The disease must have had a name before a means for its cure was described: and the Greeks were in the habit of keeping these *ικτιδες* for the same purpose as we do cats,‡ so that the source of comparison would be at hand.

Suidas derives the word *icterus* from *ικτινος*, a kite:§ because, says de Haen,|| they also have jaundiced eyes.

The Latins called jaundice *morbis regius*, from the yellow colour of gold, the *Rex metallorum*, and not from the royal diet or regimen which was believed to be

* Aretæus, *On the Causes and Symptoms of Chronic Diseases*, Bk. i. chap. xv. Adams' trans. Syd. Soc. 1856, p. 326.

† C. Plinii *Sec. Nat. Hist. Lib. xxx. Cap. xi. Lugd. Bat. 1669, t. iii. p. 321.* This bird was called *galbula* or *galgula* by the Romans, and is supposed to have been the golden oriole.

‡ Dr. Rolleston (*Journal of Anat. and Phys.* 1868, Vol. ii. p. 47) is of opinion that the *ἰκτίς* performed the same office in Greek houses as the *felis domestica* in ours, viz. that of killing mice. The *ἰκτίς* appears to be the yellow-breasted marten; and not a ferret, as some writers state.

§ Suidas, *Lexicon*, t. ii. ed. Kuster. Cantabrig. 1705.

|| De Haen, *Prælectiones*, Viennæ, 1780, t. ii. *Tract. de vermibus*, etc. p. 108. Villeneuve gives also another derivation: "quelques-uns font dériver la dénomination dont il s'agit d' *ἰκτίς*, *ἰακτινός*, (sic) espèce de mouches de bois dont les yeux sont de couleur jaune." (*Dict. d. Sci. méd.* Paris, 1818, t. xxiii. p. 386.)

good for the patient.* For the same reason, another Latin synonym is *aurugo*, or *aurigo* from *aurum*, gold. Also *morbus arcuatus*, seu *arquatus*, from the circles seen by the jaundiced.†

By the Germans, jaundice is called *Gelbsucht*, although of late years the growing custom of using words of a non-Teutonic source has made this excellent name give way almost entirely to *icterus*. By the French, *jaunisse* is almost forgotten, or thought vulgar, and *ictère* is always used.

Jaundice could hardly fail to be noticed early in the history of mankind, as the change of complexion and colour would be a striking appearance. Accordingly there is abundant mention of it in the genuine Hippocratic writings, which most often speak of it as a complication of other diseases, chiefly fevers. In the *Aphorisms* it is said to be a bad sign if the liver become hard during a jaundice; and in the third book of the *Epidemics*, that an habitual pain in the neighbourhood of the liver, with other symptoms, preceded a jaundice.‡ It may be disputed if the father of medicine conceived

* Celsus, *Medicin.* Lib. iii. cap. xxiv. "Per omne vero tempus utendum est exercitatione, frictione: si hiems est, balneo; si æstas, frigidis natationibus; lecto etiam et conclavi cultiore, lusu, joco, ludis, lascivia per quæ mens exhilaretur: ob quæ regius morbus dictus videtur." Others may think that as mental worry predisposes to jaundice, so it is called the royal disease from the anxieties of court life. It is not every one who can have the stoical virtue of Antoninus and say: "Even in a palace, life may be led well."

I have been told the very place transforms men,
And that not one of a thousand, that before
Lived honestly in the country on plain salads,
But bring him thither, mark me that, and feed him
But a month or two with custards and court cake-bread,
And he turns knave immediately. I'd be honest;
But I must follow the fashion, or die a beggar.

MASSINGER: *Great Duke of Florence*, I. i.

† Paracelsus is said to have called jaundice *morbus luseoli* from the salt which he administered in these cases; but in his writings he seems to me to have very frequently used the word *icterus* or *icteritia*.

‡ Hippocrates, *Aphorism.* Sect. vi. § 42, and *Epidem.* lib. iii. 13th patient, case of Apollonius of Abdera. Littré's ed. t. iv. p. 574, and t. iii. p. 138.

any relation between the bile secreted by the liver and the symptom of jaundice. In the other books of the Hippocratic Collection it is said that the deep yellow colour and the white colour come from the liver or disease of the liver: and in these states, the jaundices, dropsies, and leucophlegmasiæ which come from the liver are whitish, while those from the spleen are more dark.* Another white jaundice is spoken of as coming from phlegm, and attacking chiefly in the winter. Its colour is white, and the chest is filled with phlegm. The urine is white and thick.† This certainly does not correspond to what we call jaundice, nor does the second kind of jaundice described just before by the same writer. The first and the third are more like the symptom as we speak of it to-day. The first kind is caused by the bile being put in movement, and being fixed in the skin and head,‡ so that the body is as yellow as a pomegranate. The eyes are yellow, the stools white and stinking. It will be seen that some caution must be used when early writers speak of *ἰκτερος* for they do not always mean the same as we do; and like confusion has been seen almost in our own day.

Galen also asserts that the yellow bile, when it is carried all over the body, still keeping its own nature, causes a disease called jaundice.§ Aretæus says much the same thing, adding, however, that jaundice may arise from the stomach, spleen, kidneys, and colon, and is not solely formed from the liver as some have supposed.|| The jaundice caused by the liver is brought about in this fashion: if the liver and gall bladder continue to

* *Epidem.* Lib. ii. Sect. i. Cap. x. Littré's ed. t. v. p. 83.

† *De aff. int.* Cap. xxxviii. Littré's ed. t. vii. p. 261.

‡ The same view of the pathology of the disease is taken by the writer *de affect.* (Cap. xxxii. Littré's ed. t. vi. p. 245.)

§ Galen, *De med. method.* Lib. ii. Cap. i. Kühn's ed. Lips. 1826, Vol. xi. p. 74.

|| Aretæus, *On the Causes and Symptoms of Chronic Diseases*, Bk. i. Chapter xv. Adams' translation, p. 324.

secrete bile, but the passages which convey the bile to the intestine be obstructed, the bile regurgitates; it therefore becomes mixed with the blood, and the blood passing over the whole system carries the bile into every part of the body, which acquires the appearance of bile. It would be hard to express in different language the doctrine of jaundice from absorption, now universally held.

Aëtius gives the views of Galen and Ruffus; he says: Jaundice is an effusion of bile all over the body. They err who think that in all cases of jaundice the liver must be diseased. Sometimes a jaundice is caused by weakness of the gall bladder, which does not draw to itself the bile out of the liver, as it accustomed, and thus leaves the blood impure.* Paul teaches that jaundice is a diffusion of the bile all over the body, sometimes of the yellow, sometimes of the black, bile. Jaundice with fever would seem to be caused by a hot inflammation of the liver which renders the blood bilious. A jaundice without fever is caused by an affection of the gall bladder and its ducts.†

With Paul the list of the Greek and Latin writers ends, and the Arabians, to whom medicine and civilisation are so much indebted, give us a physiology but little different from that of the classical writers.

Amongst the dreams of Paracelsus will be found the statement, apparently as a reaction against the humoral pathology, that the bile never causes any disease. Jaundice is not due to the bile but to the union of three salts, "*sal entalicum, sal vitriolatum, et liquor sulphuris resoluti.*"‡

* Aëtius, *Tetrabibl.* III. serm. ii. cap. xvii. Basil. 1542, p. 582.

† Paul of Ægina, Book iii. Cap. L. Adams' trans. Vol. i. p. 580. See p. 582 for a general view of the classical writers.

‡ Paracelsus, *Opera*, Genevæ, 1658, Vol. i. p. 486. De Icteritiis. It would seem very doubtful, more so than in the case of the classical writers, what Paracelsus meant by *icteritia*. He indeed begins this book with: "*Icterus sive icteritia,*"

Sylvius de le Boe denies that obstruction in the bile ducts is an efficient cause of jaundice.* He points out that in some cases of jaundice, which he has dissected, he had found no obstruction; and further, that in some cases the stools were coloured, or but little less coloured than usual. With this writer, an important age, not merely in the history of jaundice, but in that of medicine at large, is reached. It is the time of the discovery of the circulation by Harvey, of the lacteals by Aselli, and of the thoracic duct by Pecquet. With the changes in physiology, changes in pathology likewise appear. The history of jaundice must now be broken up into three heads: i. a theory which attributes the symptom of jaundice to changes in the blood and its colouring matter, thence called hæmatogenous jaundice: ii. a theory which makes the bile to be merely separated by the liver from existing elements in the blood, not truly secreted by the liver; jaundice may thus arise when the liver ceases to excrete the bile, the elements of which accumulate in the blood and cause the general yellow appearance: iii. a theory which attributes the phænomena of jaundice to the absorption into the mass of the blood of bile already formed. Under these three heads all prevailing doctrines of jaundice may be discussed.

I. The notion of a hæmatogenous jaundice is certainly to be found in Aretæus. He speaks of divers causes of jaundice, not only from the liver, but from the stomach, the spleen, the kidneys, and the colon. But, besides jaundice from the viscera, "the general system is most powerful in producing icterus;" and "if indigestion happen in the blood, the blood assumes the

but he goes on to speak of icteritia of the brain, kidneys, and spleen; of local icteritia of the limbs, and of red, white, and black icteritia. Red icteritia seems to be erysipelas.

* Sylvius de le Boe, *Praxeos med.* Lib. i. cap. xlvi. *Opera medica*, Amstelodami, 1679, p. 301.

appearance of bile, but is distributed as nourishment to all parts, wherefore bile appears everywhere."* Galen likewise discusses the question if jaundice may be seen without disorder of the liver. He says he has seen, without any disease of this organ, a critical effusion of bile on the skin, and also that he had seen a change of blood into bile† from some strange corruption such as follows the bites of beasts, and for this he instances a case of jaundice following snake bite. This may be due to some change in the humours wrought by the poison. These ideas do not seem to have taken much root among physicians, for there seems to be no mention‡ of the theory of hæmatogenous jaundice until Bianchi again distinctly enunciated it.§ This writer speaks of two kinds of jaundice, one caused by disease of the liver, the other by a solution of the blood, in which the motions do not become white, but are rather more deeply coloured. It is more quickly brought about than the other kind of jaundice, and is seen in fevers and after the bites of vipers. This view is shared by certain obscure writers upon jaundice and bilious diseases.|| It was upheld for a time by Reil, who, under the name of polycholia, gave a long description of what is now called hæmatogenous jaundice, with rules for distinguishing it

* Aretæus, *op. cit.* p. 326. Leo, likewise, says that jaundice may arise from the conversion of blood into bile from heat of the system. (Quoted by Adams in his translation of Paulus Æginetus, vol. i. p. 585.)

† ὁρᾶται δὲ καὶ χωρὶς κρίσεως ἐκχολούμενον ἰνὸς τὸ αἷμα. Galen, *de loc. aff.* Lib. v. cap. viii. ed. Kühn, Lipsiae, 1824, vol. viii. p. 355.

‡ I have been unable to find any trace of this doctrine in the writings of Sydenham. One passage (*Obs. med.* iv. 3, § 8, *Opera omnia*, ed. Greenhill, p. 170.) is thought by Eisenmann to have a faint likeness to this teaching. To me it seems merely the explanation of a kind of dysentery by invoking a disease of the blood, the hot and acrid humours of which are thrown upon the gut by the mesenteric arteries. Nor can I find anything in Baillou's chapter on the epidemics of 1575, which would remind the reader of the theory. (*Épidémies et éphémérides*, ed. Yvaren, Paris, 1858, p. 278.)

§ Bianchi, *Historia Hepatica*, Genevæ, 1725, 3tia ed. t. i. pars ii. cap. x. p. 185.

|| For the bibliography of bilious fevers, see Eisenmann's *Die Krankheits-Familie Cholosis*, Erlangen, 1836.

from true jaundice.* The opinion was resisted by Cullen, who says that jaundice must be the result of bile, once secreted, being taken up into the blood-vessels;† by Donald Monro,‡ Eller,§ and Selle;|| they all teach that the doctrine of jaundice from absorption is the only trustworthy theory.

No further important support is met with until the time of Saunders, who speaks of the experiments of Fourcroy and Vauquelin.¶ These observers made a sort of artificial bile by heating together ox blood and water. Saunders then adds: "it would appear probable, that, under certain morbid states of the body, the blood *may* acquire a bilious appearance, independent of absorption or regurgitation from the liver."** It is worthy of note that the man, who was the first to prove by experiment the doctrine of jaundice from absorption, should likewise have given the weight of his authority to the theory of a hæmatogenous jaundice.

One of the next notices of a jaundice arising from changes in the blood, without any implication of the liver, may be found in the writings of Breschet. After pointing out the near relation which exists between melanosis and the colouring matter of the blood, he says that he presumes that jaundice is brought about much less by the bile than by the blood,†† and he attributes the jaun-

* Reil, *Tractatus de Polycholia*, Halae, 1782, p. 47. He withdrew the opinions expressed in this "*juvenile opus*," as he calls it, a few years later, and says that no bile, nor anything like bile is made, save by the help of the liver. (*Memorabil. Clinic.* fasc. iv. Halae, 1795, p. 48.)

† Cullen, *First Lines of the Practice of Physic*, § 1817.

‡ Donald Monro, *An Account of the Diseases which were most frequent in the British Military Hospitals in Germany*, London, 1764, p. 206.

§ Eller, *Obs. de cog. et cur. morb.* Venetiis, 1767, Sect. ix. p. 177.

|| Selle, *De curand. hom. morb.* Berolini, 1798, ed. Sprengel, p. 184.

¶ Fourcroy and Vauquelin, *Annales de Chimie*, 1790, t. vi. p. 181.

** Saunders, *A Treatise on the Structure, Economy, and Diseases of the Liver*, London, 1803, 3rd edition, p. 105, note.

†† Breschet, *Considérations sur une altération organique appelée dégénérescence noire, etc.* Paris, 1821, p. 21. Andral (*Clinique méd.* Paris, 1839, t. ii. p. 287.)

dice so common in the new born to changes in the circulation rather than in the liver.* Later on Virchow contributed much to the spread of this notion of an *icterus paradoxus*. He made known the likeness between hæmatoidin and bile pigment, both in crystallization and chemical reaction.† The identity of these two substances was thought to have been proved by Zenker and Funke,‡ Valentiner,§ and later still by Jaffe.|| But Städeler¶ and Holm** deny this and give rules by means of which hæmatoidin may be distinguished from bilirubin. Salkowski on the other hand, says that a substance, with many of the characters of hæmatoidin, which he found in the thyroid gland, and which must therefore have its origin in the blood, was insoluble in æther, and soluble in alkalies, which Holm and Städeler assert to be characteristic of bilirubin.†† Thudichum, however, would affirm that the body which all these observers analysed was neither bilirubin nor hæmatoidin but lutein‡‡ the hæmolutein of Piccolo and Lieben.§§ Thudichum further protests against the idea of the bile pigments being derived from hæmatoidin because they contain no iron.|||| There is, however, a hæmatin free from iron

would seem, with Breschet, to favour the notion that the colour in the newly born, or in yellow fever, is due to changes in the circulation or to a sort of general ecchymosis. The same thought is before expressed. (t. i. p. 601.)

* In the old Chinese system of physiology, the reverse was believed; the liver was the source of all the pigments in the body.

† Virchow, *Arch. f. path. Anat.* Bd. i. 1847, p. 370. See also *Ges. Abh.* Hamm, 1862, p. 849.

‡ Funke, *Lehrb. d. Phys.* Leipzig, 1860, Bd. i. p. 246.

§ Valentiner, quoted by Steiner, *Arch. f. Anat. u. Phys.* 1873, p. 163.

|| Jaffe, *Arch. f. path. Anat.* 1862, Bd. xxiii. p. 192. He obtained bilirubin from an old hæmorrhage into the brain.

¶ Städeler, *Annal. d. Chemie und Pharm.* 1864, Bd. cxxxii. p. 343.

** Holm, *Journal f. prakt. Chemie*, 1867, Bd. c. p. 142.

†† Salkowski, *Med.-Chem. Untersuch.* Hrsg. von Hoppe-Seyler, 1868, Heft. iii. p. 436. Hoppe-Seyler found bilirubin in a cyst of the breast. (*Arch. f. path. Anat.* 1862, Bd. xxiv. p. 10.)

‡‡ Thudichum, *Proc. of the Royal Society of London*, 1869, Vol. xvii. p. 255.

§§ Piccolo and Lieben, *Giornale di scienze naturali ed economiche*, Palermo, 1866, Vol. ii. p. 258.

|||| Thudichum, *Zeitschrift f. rat. Med.* Bericht f. 1868, p. 223.

which is asserted to be polymeric with bilirubin; yet it seems strange that hæmoglobin should so readily part with its iron. Dr. Young found in some careful experiments under Prof. Gamgee's direction that the ash of the bile was rich in iron,* and this fact is also worthy of being kept in mind.†

Preyer seems decidedly of opinion that hæmatoidin and bilirubin are not the same bodies. He finds that the spectra of the two are altogether different; the colouring power of hæmatoidin is also much weaker than that of bilirubin.‡ It certainly does seem that no satisfactory elementary analysis of hæmatoidin has yet been made; in Robin's case it is doubtful if he had to do with hæmatoidin at all. With this exception, hæmatoidin has been examined in but very minute quantities, only to be recognised with the microscope. If the spectra be so entirely different, it will be hard hereafter to maintain the identity of the two bodies, even if the elementary analysis prove to be very similar. Mr. Sorby, however, seems to think that the spectra of bile from snails and of hæmatin are closely akin.§ It will be necessary, however, to extend this observation to vertebrates, before any result valuable to the physician can be obtained. Maly also found that the crystals of bilirubin showed under the microscope a convex appearance, like that of the section of a biconvex lens.|| The

* P. A. Young, *Journal of Anatomy and Physiology*, Vol. v. 1871, p. 158. Robin (*Comptes rendus*, 1855, t. xli. p. 506) found iron in the ash of the red matter found in echinococci cysts in the liver; about '0002 per cent. Robin calls this red matter hæmatoidin, but I venture to express a doubt as to the propriety of so naming it. The source is highly suspicious, and it is known how very often hydatid cysts communicate with the gall ducts. The percentage analysis agrees tolerably closely with that of bilirubin.

† See also the discussion of the relation between bilirubin and hæmatoidin at p. 32 of this work.

‡ W. Preyer, *Die Blutkrystalle*, Jena, 1871, p. 187.

§ Sorby, *Quarterly Journal of Microscopical Science*, 1876, Vol. xvi. p. 78.

|| Maly, *Sitzungsberichte der math.-naturw. Classe d. kaiserlichen Akademie*, Wien, 1868, Bd. lvii. Abth. ii. p. 97.

crystals of hæmatoidin have always a rhomboidal appearance.

The notion of the identity of bilirubin and hæmatoidin being once set up in the minds of physiological chemists, it seemed no strange statement that the bile pigments should appear in the urine when any large number of the blood corpuscles were dissolved. This indeed is what Frerichs found after the injection of the bile acids into the blood, a fact explained by him in altogether another way.* Kühne, likewise upheld Frerichs' belief, and added a new fact, that the bile pigments appear in the urine after the injection of hæmoglobin into the circulation.† M. Herrmann also found these after the injection of large quantities of water into the veins;‡ Nothnagel, after the injection of æther and chloroform;§ Munk and Leyden, after the injection of phosphoric acid:|| all these bodies having the power of dissolving the red blood-corpuscles and thus setting the hæmoglobin free in the blood-vessels.

The theory of hæmatogenous jaundice seemed thus to receive great support from experiment.

But it was assumed with too great haste that if the colouring matter of the bile were present in the urine, that jaundice was thus of necessity at hand. It is indeed true that the urine is often the first to give notice of a coming attack of jaundice, even before the conjunctiva; but it is well to point out with Virchow¶

* Frerichs, *Klinik d. Leberkrankheiten*, Braunschweig, 1858, Bd. i. p. 405. See also *Arch. f. Anat. u. Phys.* 1856, p. 59, note.

† Kühne, *Arch. f. path. Anat.* 1858, Bd. xiv. p. 337. See also *Lehrb. d. phys. Chemie*, Leipzig, 1866, p. 89.

‡ M. Herrmann, *De effectu sanguinis diluti in secretionem urinæ*, Diss. Inaug. Berolin. 1859, p. 23.

§ Nothnagel, *Berliner klin. Wochenschr.* 1866, p. 31.

|| Munk and Leyden, *Die acute Phosphorvergiftung*, Berlin, 1865, p. 129.

¶ Virchow, *Arch. f. path. Anat.* 1865, Bd. xxxii. p. 120. Poncet has attempted to cause jaundice by the injection of blood under the skin of animals; he found a high-coloured urine was passed, but strange to say, no chemical tests were used. (*de l'ictère hémétique traumatique*, Thèse de Paris, 1874, p. 61.)

that in none of these experiments has a real jaundice been brought about. There has never been a yellow staining of the tissues, but only a reaction of bile pigment in the urine; and between these two states there is a deep and wide division. No artificial jaundice has been as yet caused by injecting any quantity of bile into the blood,* though it would seem possible that jaundice might follow, if substances which destroy the blood-corpuscles were allowed slowly to act upon the œconomy.

The likelihood of this last observation of Virchow's to be true has of late years somewhat decreased. The foregoing experiments upon which so much stress has been laid have been repeated, and in general, no bile pigment has been detected in the urine after the injection of substances which dissolve the blood-corpuscles. Naunyn was the first to repeat these observations† and he could not succeed in obtaining a reaction peculiar to the bile pigment after the injection of hæmoglobin into the circulation or under the skin. In both cases the urine might contain blood colouring matter, but no bile pigment. J. Steiner, likewise, repeated M. Herrmann's observations, and found that no bile pigment was present in the urine after the injection of large quantities of water.‡ I myself have been unable to detect the presence of bile pigment in the urine after the injection

* Dr. George Harley indeed states that he has succeeded in making a dog jaundiced by injecting the bile of other dogs under the skin. He failed, however, in two other experiments. (*Jaundice: its pathology and treatment*, London, 1863, p. 96.)

† Naunyn, *Arch. f. Anat. and Phys.* 1868, p. 410.

Nasse (*Sitzungsberichte d. Marburg. Gesellschaft*, 1875, No. 2. quoted in Hayem's *Revue des Sciences méd.* 1876, t. vii. p. 530) found that the urine gave no reaction with nitric acid after the injection of large quantities of blood into the stomach of dogs; but (Hofmann and Schwalbe's *Jahresb. d. Anat. u. Phys.* f. 1874, iii. Abth. p. 182.) the same observer is reported to have found that after injecting a great quantity of dissolved corpuscles into the stomach of one dog, the urine shows traces of bile pigment on the second and third day, not the first.

‡ J. Steiner, *ibid.* 1873, p. 160.

into the circulation of the bile acids, notwithstanding the statements to the contrary of Frerichs and Kühne. Furthermore, Naunyn, after the injection of æther under the skin found well-marked signs of the presence of hæmoglobin in the urine in all cases; but in only one out of four could a certain opinion be given as to the presence of bile pigment.*

This great difference between observers so trustworthy may, I think, best be explained by the fact that Frerichs, Kuehne and Herrmann seemed to have used for their experiments dogs, in whose urine a substance which gives all the reactions of bile pigment is an almost constant constituent.† Naunyn, Steiner and myself have used rabbits exclusively for experiment, and in the urine of these animals, unless fasting, bile pigment is not often seen. These later experiments would therefore seem more trustworthy than those of Kühne and Frerichs, and I do not think that their value has been destroyed by Tarchanoff's recent observations, for although after the injection of hæmoglobin into the circulation bile pigment was seen in the urine, yet the experiments themselves are not such as to command confidence. In the first place, dogs were used, in some cases even without testing the urine beforehand for bile pigment; and further it was not expressly stated that the animal was not fasting, and most of the experiments lasted over six hours, at the end of which the bile pigment was found.‡ Even this observer found no bile pigment after a six-hours narcosis from chloroform.

Although Breschet was the first to found the doc-

* Naunyn, *op. cit.* p. 438.

† But this does not explain the matter throughout: Nothnagel used rabbits in all his experiments with æther and chloroform (*Berlin. klin. Wochenschr.* 1866 p. 31) and Kühne (*Lehrb. der phys. Chemie*, p. 89) expressly says that rabbits must be used in the hæmoglobin-injection experiment on account of the constant presence of the bile pigment reaction in the urine of dogs.

‡ Tarchanoff, *Arch. f. d. ges. Phys.* 1874, Bd. ix. p. 53.

trine of a hæmatogenous jaundice, supported by Andral, and more lately by less-known names, yet the theory seems to have made little progress in France; and in England the doctrine is but little received, the other view, that of jaundice from suppression, finding greater favour. It is chiefly invoked to explain the phænomena of *icterus gravis*. Under this head may be placed acute yellow atrophy of the liver, the jaundice seen in poisoning from phosphorus, in pyæmia, and other acute diseases. In this way Leyden has laboured to explain the yellowness of the skin sometimes seen in chlorosis, pyæmia, heart disease, or after anæsthesia from chloroform. In these cases the yellowness of the skin is out of all proportion greater than the bilious appearance of the urine. In jaundice from obstruction, the reverse is seen. There is likewise no evidence of the presence of bile acids in the urine in these cases. Further, there is often proof, in the cases of *icterus gravis*, of the circulation of some poison in the blood, able to destroy the red corpuscles, as in poisoning by phosphorus, yellow fever, and the like. The varieties of *icterus gravis* resemble each other in having a tendency to stupor or delirium. In the fatal cases, no impediment can be found, after death, to the flow of bile into the duodenum, the liver itself being free from a jaundiced tint and the fæces containing bile. A far advanced fatty degeneration of all the glandular and muscular organs is likewise found.*

I should long hesitate in forming any opinions from the statement that the urine is often less jaundiced than the skin, or that the liver after death shows no jaundiced appearance. Virchow, for instance, formerly thought that a jaundice of the liver preceded a jaundice of the whole body,† but later saw reasons

* Leyden, *Beiträge zur Pathologie des Icterus*, Berlin, 1866, p. 6.

† Virchow, *Arch. f. path. Anat.* 1847, Bd. i. p. 380.

to withdraw this opinion,* and this admission is of the greater importance, since Virchow was undoubtedly the founder in modern times of the doctrine of hæmatogenous jaundice. Nor can I attach much weight to the statement, that in cases of slight jaundice, the urine is much less jaundiced than the skin. I have sometimes found in examining cases of slight jaundice after death, that the serous effusions from the chest and belly gave an intense reaction with nitric acid, while the urine gave but slight indications of the presence of bile pigment with the same reagent. The serous effusions and the urine may, I should think, be looked upon as at least equal in importance for indicating the amount of bile pigment contained in the blood. The cases which I mention have been chiefly those of heart disease.

A point of which much importance has been made by Leyden, is the absence of the bile acids in the urine, in some cases of jaundice. Naunyn's observations have, however, destroyed all value which may be attached to this opinion, for he has shown that the bile acids may be found in every urine, even in that of perfect health.† They appear to be absent in no cases of jaundice, except perhaps at the end of cases of long continued obstruction to the bile ducts, as Golowin has pointed out.‡

It is indeed only from the fatal cases that any safe conclusions can be drawn. The fatal cases of which Leyden speaks all belong to the class of *icterus gravis*. Poisoning by phosphorus would, I think, be accepted as a type of this class. The stools are sometimes coloured, sometimes free from colour. Yet Oskar

* Virchow, *Arch. f. path. Anat.* 1865, Bd. xxxii. p. 121.

† Naunyn, *Arch. f. Anat. und Phys.* 1868, p. 430.

‡ Golowin, *Arch. f. path. Anat.* 1871, Bd. liii. p. 433.

Wyss* and Ebstein† found in the livers of dogs and men poisoned by phosphorus, that the finer ducts within the liver were plugged with a colourless mucus which hindered the descent of the bile ; a plain cause of jaundice. While this explanation of the jaundice remains available, it seems to me imprudent, to say the least, to search for other and less likely causes elsewhere.

The presence of deeply coloured stools cannot always be received as proof of the freedom of the hepatic ducts. Indeed, in jaundice, the more deeply coloured the stools, the greater suspicion should be aroused. It is well known that many substances given by the mouth make the stools dark, as charcoal, iron, or bismuth. What is more important in the present discussion is that blood passed into the alimentary canal causes the stools to have a very high colour ; now in *icterus gravis* hæmorrhages are very common and especially abundant in the stomach and intestines. It is therefore not surprising to find that in many cases the stools are reported to be dark. In a case of my own, I found that the fæces in the large intestine were clay-coloured ; in the small intestine they were dark, almost black. In jaundice I look upon the absence of colour in the stools as tolerable proof that some of the bile ducts are obstructed ; but I cannot accept the presence of colour in the stools as proof that the ducts are free.

As Leyden has been the champion of hæmatogenous jaundice in Germany, so Gubler has been in France. In 1857 he published a case of poisoning by lead, complicated with jaundice. The urine was very high coloured, and to the eye alone presented precisely the appearance

* Oskar Wyss, *Arch. d. Heilkunde*, 1867, p. 469.

† Ebstein, *ibid.* p. 506 ; and 1869, p. 379. I have myself verified the statement that the smaller ducts may hold bile, the larger a colourless fluid. (*Trans. of the Path. Soc.* 1874, Vol. xxv. p. 161.)

of ordinary jaundiced urine. It gave, however, no distinct reaction with Gmelin's test, and Gubler from this single circumstance calls the case one of *ictère hémophéique*.* There is, strange to say, no account of the state of the stools; so the case proves nothing. The same strange disregard of an important appearance runs through the table of elaborate distinctions given by Michel, a pupil of Gubler, the theory of which may be at any moment upset by an inspection of the *fæces alvinæ*.† The cause of this kind of jaundice is, according to Gubler, the inability of the liver to separate from the blood the colouring materials for the formation of bile, when from some cause or other there is too rapid destruction of the red globules. This blood pigment, free in the blood, Gubler calls hæmophæin.‡ This is evidently a revival of the old doctrine of suppression, allying itself to the newer theory of hæmatogenous jaundice. It is used to explain the jaundice in febrile disorders and of the new born, as well as that which follows catarrh of the stomach.§ Gerhardt endorses many of Gubler's opinions. He calls the pigment in the urine urobilin,

* Gubler, *Union méd.* 1857, p. 503. Hæmaphæin is the name used by Franz Simon for the natural colouring matter of the urine, and which he believed to be derived from the red blood corpuscles. (*Animal Chemistry*, Sydenham Society's Translation, 1845, Vol. i. p. 159, and Vol. ii. p. 119.)

† Evariste Michel, *de l'ictère hémaphéique*, Thèse de Paris, 1868, pp. 14, 16, and 18. In the cases there is also no word about the stools. Dreyfus-Brisac, another disciple of Gubler's, does indeed at the end of his table of distinctions mention that the stools in hæmaphæic jaundice are: *très-variables, parfois un peu décolorées, le plus souvent très-colorés*; (*De l'ictère hémaphéique*, Paris, 1878, p. 40) but in his cases he seems to have paid very little attention to the stools at the height of the disease, and only when the jaundice is fading does he remark how deeply coloured they are; a state which may readily be explained without resorting to Gubler's hypothesis.

‡ Rendu gives a just account of Gubler's views in an excellent article in the *Dictionnaire encyclopédique des Sciences méd.* Foie (pathologie) 4e Série t. ii. p. 680.

§ Laborde praises Gubler highly: "M. Gubler, il faut bien le dire, l'a faite complètement sienne par la précision apportée dans l'analyse des faits, l'exacte appréciation des phénomènes, et les développements qu'il n'a cessé de lui donner, en prenant pour base les faits cliniques." (*Physiologie pathologique de l'ictère*, Thèse pour l'agrégation, Paris, 1869, p. 69.)

but solely because the extract of the urine with chloroform gives a fluorescence into green-yellow when treated with choride of zinc and ammonia.*

Poncet has also published a thesis in which he attempts to establish a jaundice from the destruction of the blood corpuscles after great extravasations of blood. This observer is of opinion that hæmatogenous jaundice can no longer be denied. He has seen, after great extravasations of blood in the limbs or trunk, a slight jaundice arise. This jaundice he says is due to the destruction of the red corpuscles, and the increased colour of the urine is due solely to an increase of the urobilin. Nothing here, too, is said of the state of the stools. Poncet only brings forward one case examined after death; and in this, strange to say, no account of the liver seems to be recorded.† This writer adds but little to the evidence already given in favour of hæmatogenous jaundice: and a word of warning has been addressed to him by Paul Cazeneuve who could find no increase of the colouring matters of the urine, nor any bile pigments in the urine after the subcutaneous injection into a rabbit of 10 to 20 C. C. of blood, or ·05 to ·1 grm. of hæmatin.‡

The following case, which Immermann calls one of hæmatogenous jaundice, is certainly well worthy of attention.

Christian Rupaner, aged 23, born in Baden, was admitted into the Hospital at Basel on January 23. 1873. For eleven days before, he had been suffering from symptoms of a moderately severe attack of typhoid fever. The course of the disease was regular and uncomplicated; it was treated with quinine in large doses,

* Gerhardt, *Correspondenz-Blätter des allgem. aerzt. Vereines von Thüringen*, 1878, Jahrg. vii. No. ii. Nov. 20.

† A. Poncet, *de l'ictère hématique traumatique*, Thèse de Paris, 1874, p. 40.

‡ P. Cazeneuve, *Gaz. méd. de Paris*, 1877, p. 271.

and with baths as often as the temperature rose. On Feb. 21. there was a relapse, treated as the first attack. On Feb. 27. the urine was slightly albuminous and contained pus cells. On March 1st a slight jaundiced tint began about 7 a.m. and at 9. a.m. the tint was deep; liver natural. Continual vomiting of bilious matter and two highly bilious stools in the course of the morning. At the same time the urine was scanty and almost black. It gave no trace of bile pigment, but became almost solid on boiling, and showed Heller's test for blood. Under the microscope no red corpuscles, only pus corpuscles were seen. On March 2. the jaundice was the same; vomiting, four bilious stools. The urine albuminous as the day before, no red blood corpuscles in sediment but some well preserved pus corpuscles. With the spectroscope, oxyhæmoglobin and hæmatin were in the urine; no bile pigment. On March 3. the jaundice of skin and conjunctiva much decreased. Vomiting continued with diarrhœa and bilious stools. The urine yellow brown, highly albuminous, containing neither blood colouring matter nor bile pigment. On March 4. jaundice gone; vomiting and albuminuria continuing till death. On March 9. the patient died comatose, no jaundice and no blood in water being again seen. After death the kidneys were found in a state of acute parenchymatous degeneration. In the small intestine bilious fluid; on pressing the gall-bladder, a hyaline plug escaped from the gall ducts into the duodenum. The lower part of small intestine showed freshly-healed typhoid changes. In the liver there was some over growth of the connective tissue.*

The reader should note, in forming a judgement on this case, that the liver and the ducts were not free from disease. The liver was in an early stage of cirrhosis,

* Immermann, *Deutsches Arch. f. klin. Med.* 1874, Bd. xii. p. 502. The case is fully given.

and the extremity of the gall duct held a plug of mucus. It is true that no bile pigment was found in the urine, but it is possible that the large amount of albumen present in the urine may have had the effect of masking the ordinary Gmelin's reaction. Bile acids were not looked for.

The grounds on which the theory of hæmatogenous jaundice have been set up are, to my mind, altogether insufficient. It cannot be said that the origin of the colouring matter of the bile from that of the blood is proved; indeed of late the course of discovery has been rather against their identity than in favour of it. And until it have been shown that bile pigment has its source in the blood-corpuscles, it will be the duty of the practical physician to reject the theory of hæmatogenous jaundice.

II. The second kind of jaundice is that of jaundice by suppression. The great doctors of the seventeenth, and early part of the eighteenth, centuries, taught that the secretions existed ready formed in the blood, and that the glands merely acted as filters to strain the excretions from the circulating mass. Glisson speaks thus of the liver.* The doctrine of jaundice from suppression of the secretion was a natural outcome of this physiology. It is therefore to be found in the writings of Morgagni, who distinctly attributes the jaundice in case of obstruction not to the absorption of bile already secreted; but, because the bile ducts are already filled by secretion, the bile cannot enter them, and thus accumulates in the blood.† Van Swieten, likewise, speaks of two kinds of jaundice; one from an impediment to the free exit of the bile from the bile ducts; the other, from a hindered secretion.‡ Towards the end of the eighteenth century, this view of jaundice

* Glisson, *Anat. Hepat.* Cap. xxxviii. et seqq. Amstelædami, 1659.

† Morgagni, *De sedibus, etc.* Ep. xxxvii. Art. 9.

‡ Van Swieten, *Comment.* § 950, Lugd. Bat. 1755, t. iii. p. 127.

began to lose ground, even before the experiments of Saunders. It continued, however, to be taught and acted on by many noted physicians.

Andral,* Sir Thomas Watson,† Bamberger,‡ Griesinger§ and Trousseau|| have all supported the doctrine of jaundice by suppression. Dr. Budd¶ considers this kind of jaundice to be by far the most common. He believes, however, that the colouring matters only are made in the blood, while the bile acids are formed in the liver itself; a view which is supported by Skoda** and Dr. George Harley.†† But about the date of the publication of the first edition of Dr. Budd's book, the doctrine of the formation of the bile in the blood fell into discredit with physiologists, and in our own day, with the exception of one or two supporters, is universally disbelieved. With this, as a matter of course, the notion of a jaundice from suppression of secretion fell too.

The turn of the tide of medical opinion may be noted when Liebermeister, fifteen years ago, pointed out that he did not think the doctrine of the non-existence of the elements of the bile in the blood so surely proved as others then thought. One of his reasons is that jaundice sometimes breaks out after the liver cells have completely disappeared. §§ There is no proof,

* Andral, *Clinique méd.* Paris, 1839, t. ii. p. 286.

† Thomas Watson, *Lectures on the Principles and Practice of Physic*, Lecture lxxv. London, 1857, Fourth ed. Vol. ii. p. 602. He says that Darwin was the first to introduce into this country the doctrine since supported by Chevreul and Mayo. Erasmus Darwin (*Zoonomia*, Lond. 1801, Vol. ii. p. 5) speaks of a paralysis or inability of the secretory vessels of the liver, but without bile in the stools or urine, and a skin like the colour of full-grown silkworms. It may well be doubted if he speak of a jaundice.

‡ Bamberger, *Krankheiten des chylopoëtischen Systems*, Erlangen, 1857, p. 517.

§ Griesinger, *Infectionskrankheiten*, Erlangen, 1857, p. 78.

|| Trousseau, *Clinique méd. de l'Hôtel Dieu*, Paris, 1865, 2e éd. t. iii. p. 274. His opinions expressed elsewhere make it doubtful if he always held this belief.

¶ George Budd, *On Diseases of the Liver*, London, 1845, p. 373.

** Skoda, *Deutsche Klinik*, 1859, p. 286.

†† George Harley, *Jaundice*, London, 1863, p. 20.

§§ Liebermeister, *Beiträge zur path. Anat. u. Klinik d. Leberkrankheiten*, Tübingen, 1864, p. 241.

however, that this statement of Liebermeister's is correct. No doubt he has shown that in a large number of cases, hitherto unsuspected, the liver cells are destroyed; in many cases of pyæmia, puerperal and typhoid fever: but I do not think he has proved that the jaundice has ever arisen after the complete destruction of the secreting tissue of the liver. Some writers have thought that acute yellow atrophy affords the best proof that the bile is made in the liver, because towards the end of the disease, as the liver cells are destroyed, but little pigment is found in the urine, and no bile acids.*

Dr. Moxon thinks that the colourless contents of the ducts in cases of long continued obstruction prove that the bile is not formed in the liver, and that all cases of jaundice are caused by suppression of the secretion, not by reabsorption of secreted bile.† His views closely resemble those of Morgagni quoted above, but it cannot be thought that he has brought forward much evidence in favour of his belief.

Jaccoud is inclined to the belief that in long-continued jaundice the liver ceases to secrete bile.‡ To this view there is but little physiological objection; for it is not improbable that a liver severely damaged should cease to secrete bile, and that the jaundice should thereupon decrease. It is very different to the statement that jaundice may be caused by suppression of the functions of the liver.

The theory that the bile was not formed by the liver was thought to have been disproved by Johannes Mueller, Kunde, and Moleschott§. This last observer found that frogs, after their liver had been taken away,

* Hilton Fagge, *Guy's Hospital Reports*, 1875, p. 174.

† Moxon, *Trans. of the Pathological Society of London*, 1873, Vol. xxiv. p. 133.

‡ Jaccoud, *Leçons de Clinique méd.* (Lariboisière) Paris, 1873, p. 543.

§ See p. 83 of this work.

lived nearly three weeks, and yet no trace of bile could be found in the blood, muscles, gastric juice, lymph, or urine. The vital processes in these cold-blooded animals are, however, but slow. Leyden tied the common duct of frogs, and after 8 to 14 days found no trace of jaundice in the liver,* so that if no jaundice be caused by ligature of the common duct, it would not be strange that none should arise after the taking out of the liver. If these experiments of Leyden's be trustworthy, a very important support to the view that the liver forms the bile is taken away.

Another fact thought to favour this last view is that the bile acids and bile pigments cannot be found in the blood, even in the blood of the portal vein. Of this last there is usually so little to be had that there is scarcely enough for a trustworthy analysis. But I believe that no observer in modern times has been able in health with certainty to detect any of the elements of the bile in the blood. Naunyn, however, has found small but appreciable amounts of bile acids in the urine of healthy men:† and it is no uncommon thing to find that the urine of men and dogs shows traces of the presence of bile pigment: and this is especially the case after long fasting, when, that is to say, the liver has not for some time been stimulated to excrete much bile. It may further be alleged that if the elements of the bile be formed in the blood, it would be unlikely that they should be found in the serum. The liver seems, as shown by the experiments quoted just above, to have the power of rapidly secreting into the bile ducts all the bile pigment and bile acids which may be brought into the blood. On the other hand it may be pointed out

* Leyden, *Beiträge zur Path. des Icterus*, Berlin, 1866, p. 19. He does not, however, expressly say that he examined the blood or urine; nor does he say that he fed the animals, a point of importance in judging of matters allied to the digestion and general powers of life.

† Naunyn, *Arch. f. Anat. u. Phys.* 1868, p. 430.

that Schmulewitsch has succeeded in keeping up a continuous secretion of bile for two or more hours after death by causing the same blood to pass and repass many times through the liver, a phænomenon opposed to the notion that the bile is simply separated by the liver.* Pflüger has, however, repeated Schmulewitsch's experiments in a dead liver with three *per cent.* saline solution, and has found an apparent abundant secretion of bile. He thinks there is no real secretion of bile, but a transudation into the ducts pushing the bile already made before it.† Röhrig has repeated both Schmulewitsch's and Pflüger's experiments, and finds that bile is secreted when blood is passed through the vessels, while none flows out when saline solution is used.‡

The presence also of a small quantity of the bile pigments and bile acids in the urine may be explained by supposing that they have been absorbed from the bile passages after secretion. Such was the belief of Dr. Bence Jones,§ who says that the bile begins to pass out of the gall bladder as soon as it is passed into it. Of this statement it must be admitted, however, that very little direct proof exists.

Some authors, especially Dr. Murchison,|| have looked upon the fact that in some cases of diseased livers without jaundice, no bile can be found in the

* Schmulewitsch, *Arbeiten aus der phys. Anstalt zu Leipzig*, iii. Jahrg. 1868, p. 113.

† Pflüger, *Arch. f. d. ges. Phys.* 1871, Bd. iv. p. 54.

‡ Röhrig, *Stricker's Med. Jahrb.* Wien, 1873, p. 267.

§ Bence Jones, *St. George's Hosp. Reports*, 1866, Vol. i. p. 190.

|| Murchison, *Clinical Lectures on Diseases of the Liver*, London, 1868, p. 305. I think these cases of colourless mucus in the bile passages without jaundice are somewhat rare. Upon Haspel's cases (*Maladies de l'Algérie*, Paris, 1850, t. i. p. 262) I think much weight can scarcely be laid. He is speaking of abscess of the liver in which there was almost complete destruction of the organ. He adds that the bile was no longer secreted, and the bladder contained only a little white mucus. He does not speak of the state of the other bile passages. See also cases reported by Andral, (*Clinique méd.* Paris, 1839, t. ii. p. 275.) Frerichs, (*op. cit.* Bd. i. pp. 86 and 322.) and Wertheimber. (*Fragmente zur Lehre vom Icterus*, München, 1854, p. 3.)

bile ducts, as evidence in favour of the view that the bile is formed in the liver. Dr. Hilton Fagge, in a paper lately published,* admits that this would be good evidence, were the liver diseased in all the cases in which the bile ducts were unstained. He then quotes Dr. Moxon's authority for saying that in only one out of four such cases observed by him, was the liver diseased,† the other three being cases of pyæmia and pneumonia. The liver is so commonly diseased in these two morbid states, and as commonly overlooked, that it would be desirable to have further evidence as to the state of the liver, before deciding that the liver is not always diseased when the ducts are free from colour.

Gubler, according to his interpreter Michel, appears to have formulated a theory of jaundice which unites the idea of suppression of the functions of the liver with a change in the blood. Michel, giving inedited tables of Gubler's,‡ says: "The exciting cause of hæmaphæic jaundice is an inability, absolute or relative, of the liver to separate from the blood the materials destined for the formation of bile, and especially the colouring matter derived from the destruction of the globules and to which Gubler gives in general the name of hæmaphæin. The proportion of this colouring matter, the source of that of the bile, being normal, the liver sometimes falls into a state of torpor, or the liver continuing its functions, the destruction of the globules becomes sometimes excessively rapid, and brings into the circulation waste material which the liver cannot transform.

"The remote causes of this kind of jaundice would

* Hilton Fagge, *Guy's Hospital Reports*, 1875, p. 172.

† Moxon, *Trans. of the Path. Soc. of London*, 1869, Vol. xx. p. 220.

‡ Apparently derived from *αἷμα* and *φαιός*, dusky dun, grey, Latin *fuscus*. (See Simon, *Animal Chemistry*, 1845, Sydenham Society Trans. Vol. i. p. 42.) *Ictère hémophéique* appears as the title of a case by Gubler in the *Union méd.* for 1857, p. 503.

thus be those which paralyse the secreting functions of the liver, either by preventing the bringing to this organ of materials upon which it acts, or by striking the parenchyma with inertia. Thus hæmaphæic jaundice is seen most commonly in acute phlegmasiæ with rapid destruction of the red corpuscles: such as pneumonia, acute rheumatism, in poisonings, such as yellow fever, pyæmia, agues: in the *embarras gastrique* and the jaundice of the new born."

Gubler, according to the same author, looks upon the following appearances as diagnostic of this variety of jaundice, as distinguished from that caused by a hindrance to the flow of bile: The tint of the patient slight, sometimes deep, but in every case a little dull; no itching or exanthemata; the serum of the blood and closed cavities, when acted on by nitric acid, shows a brown colour; the slow pulse is but a temporary symptom, seen in convalescence; the urine is an amber red or like strong tea; it stains linen reddish; which, when dried, is of the colour of salmon or weak rhatany decoction; of feeble dyeing power; nitric acid gives a colour, more or less deep, of brown red, and gives no precipitate of biliary resin, ordinarily taken for albumen.*

The views of Gubler seemed to have been based on a case of lead colic, in which jaundice was a well-marked symptom.† It is therefore the more noteworthy that, in this case, upon which so much depends, no record should appear of the state of the stools. The views of this observer seem to me so crude and ill-digested that I do not think it will be worth while further to discuss them.

It will be seen that very little evidence as to the place in which the bile pigments and bile acids are formed is

* Michel, *De l'ictère hémaphéique*, Thèse de Paris, 1868, pp. 14, 16, and 18. Cf. Laborde, *Physiologie pathologique de l'ictère*, Thèse de Paris, 1869, p. 91.

† Gubler, *Union méd.* 1857, p. 503.

in existence ; but that what little evidence there is may be cited in favour of the view that these bodies are formed in the liver. This being the case, physicians have no right to found a theory of jaundice which demands a contrary physiological theory, for theories in medicine must be framed in consonance with those views for which there is the greater evidence.

III. The third theory of jaundice is that which attributes this symptom to the absorption into the blood of bile already excreted by the liver. It is beyond all doubt the best founded of the theories of jaundice ; and the one to which the morbid anatomist, as well as the experimental pathologist, will be the most inclined ; as in the great majority of cases of jaundice which are examined after death, some obstruction to the flow of bile into the duodenum is undoubtedly found.

It has been seen that, very early in the history of medicine, obstruction to the bile ducts was looked upon as a cause of jaundice. No distinction, however, was made between the effects of an obstruction to the hepatic and the cystic duct ; and Morgagni had to teach that the cystic duct could be obstructed without jaundice being caused. This writer did not, however, look upon the absorption of secreted bile as the cause of jaundice. He thought that the bile was unable to pass from the liver into the ducts, these being already over-filled, and that jaundice was caused by suppression of secretion. This doctrine, however, was overthrown at the end of the last century by the experiments of Saunders. He threw a ligature around the bile duct of a dog ; it was killed in two hours after. A bilious coloured fluid was seen in the absorbents around the parts and near the thoracic duct. The serum of the blood taken from the jugular vein gave a yellow tinge to white paper dipped in it ; much less, however, than the serum from the hepatic veins, the deeper

colour of which was well-marked.* From these two experiments Saunders thought that it was proved that the absorbents as well as the hepatic veins are concerned in the bringing forth of jaundice.†

For nearly a hundred years this theory of jaundice from absorption has held its own, and been assented to by every physician and pathologist who has written on the subject. Among the theories of jaundice it is the only one grounded upon observation and experiment, and the only one to which universal assent may be demanded.

The kinds of jaundice from absorption have been described:

- i. Jaundice from obstruction of the ducts.
- ii. Jaundice from absorption of the bile when the pressure in the blood-vessels of the liver is decreased.
- iii. Jaundice from incomplete destruction of the bile absorbed into the blood.

i. It is well known from the experiments of Heidenhain that the pressure under which bile is excreted is extremely small.‡ In guinea pigs, the bile ceases to flow down the ducts when opposed by a column of water only 20 centimeters high, and prefers to pass

* Saunders, *A Treatise on the Structure, Economy, and Diseases of the Liver*, London, 1803, 3rd ed. p. 111.

† Lately repeating Saunders' experiment, I was unable to arrive at the same results as he did. (*St. Bartholomew's Hospital Reports*, 1873, vol. ix. p. 176.) Frerichs likewise (*op. cit.* Bd. i. p. 99) says he has been unable to discover any bile pigments in the blood, serum, or lymphatics, twenty-four hours after the ducts have been tied. Saunders seems to have tied the hepatic duct; in my own experiment the common duct was tied. I have no doubt of the general accuracy of Saunders' conclusions.

‡ Friedländer and Barisch, *Arch. f. Anat. Phys. &c.* 1860, p. 666. Kowalewsky (*Pflüger's Arch. f. d. ges. Phys.* 1874. Bd. viii. p. 597.) found the pressure of the bile in woorarised cats somewhat higher, from 12 to 20 mm. of mercury; and varying, in direct ratio, with the arterial blood pressure. There is another very instructive experiment of Heidenhain. (*Stud. des phys. Instituts zu Breslau*, 1868. Heft. iv. p. 232.) He allowed a solution of indigo-carmin to flow under small pressure into the bile ducts: the mucous membranes, especially the conjunctiva, of the animal soon became blue; the urine likewise.

into the circulation. It will be seen from this fact how little obstruction to the passage of the bile into the duodenum is needed to cause the bile to flow back into the blood. Nor is it necessary that the obstruction should be complete, but merely that the bore of the duct should be narrowed enough to cause the bile to pass with some trouble into the bowel. It would almost seem that the bile passes as readily into the circulation as into the duodenum. Thus jaundice may easily be caused by a hyperæmic or catarrhal swelling of the part of the common duct which passes through the walls of the duodenum, and yet after death all trace of swelling will have disappeared, and the duct will be fully patent. The only proof of the existence of an obstruction is the finding of the part of the duct below the obstruction uncoloured by bile. Even this evidence may be wanting if the examination have not been made with care enough; for the least pressure on the gall-bladder will send the bile down the common duct into the bowel, staining the duct of a bilious colour. More obvious causes, such as the presence of a calculus in the duct, or the pressure of a tumour from the outside, need not here be spoken of.

ii. The second kind of jaundice from absorption is that which takes place when the pressure of the blood in the vessels of the liver is decreased. This is Frerichs' theory of jaundice. He says that, of the two products of the liver cells, bile and sugar, one passes into the hepatic vein, the other into the capillary bile ducts. The flow of fluid towards the blood can only take place by diffusion; towards the bile ducts, by filtration. How the two are separated is unknown. It must be assumed either that the rapidity of the diffusion into the blood of the elements of the bile is greater than that of sugar; or that the sugar has some attraction to some element of the blood which is want-

ing to the bile. This last hypothesis is improbable, for no constituent of the blood is known to possess an attraction for sugar. On the first hypothesis, the separation of the two substances would be incomplete; some of the bile passing into the blood, and some of the sugar into the bile; which, indeed, is really the case.* If, therefore, the pressure of the blood upon the sides of the vessels in the liver be decreased, the bile will pass in that direction where there is least resistance, that is, into the circulation, and thus jaundice will arise.† Heidenhain has given experimental evidence of the truth of this hypothesis. He found that on decreasing the pressure of the blood in the vessels of the liver, the bile already formed began to pass into the circulation.‡ Frerichs would in this way explain the jaundice seen in cases of plugging of the portal vein, in cases of pigment liver, where a part of the capillaries is filled by masses of pigment, the jaundice seen in the new-born, and after bleeding from the roots of the portal vein, as in yellow fever. This theory of jaundice must undoubtedly be allowed a place equal in probability to that of jaundice from obstruction. It may prove serviceable hereafter in explaining the jaundice which so suddenly arises after mental emotions, the bites of serpents, and after great general bleeding.§

iii. The last theory of jaundice which remains to be discussed, is that which attributes the symptom to incomplete destruction of the bile absorbed into the blood.

* C. Ludwig, *Lehrb. d. Phys. des Menschen*, Leipzig and Heidelberg, 1856. Bd. ii. p. 232.

† Frerichs, *op. cit.* Bd. i. p. 89.

‡ Heidenhain, *Studien des phys. Instituts zu Breslau*, Leipzig, 1868. Heft. iv. p. 238.

§ In this way I should be inclined to explain the jaundice seen in the two first cases recorded by Mr. William Smith. (*Brit. Med. Journal*, 1869. Vol. ii. p. 5.) The jaundice appeared on the first and fifth days after great general bleeding. The stools were light coloured. In the two last cases I feel scarcely disposed to connect the bleeding with the jaundice.

In health the greater part of the bile pigment and bile acids poured into the duodenum is taken up again during the passage of the food through the small intestine. The bile, therefore, finds its way into the radicles of the portal vein, and undergoes a change of some kind, probably oxydation, after which it is thrown out of the system. When this metamorphosis of the bile in the blood is checked or brought to a standstill, jaundice comes on.

This theory may be found in the writings of Daniel Sennert, who speaks of an excess of bile secreted by the liver, which cannot be excreted by the accustomed passages. In this disease, he says, not only is the urine coloured saffron, but the fæces are also highly coloured. Fever is present and the hands and feet are hot.* Distinct traces of the same doctrine may be found in the writings of Cullen, who regards it with disfavour;† and in those of Portal‡ and Gardien§ who approve. Frerichs had, no doubt, some such theory in mind when he speaks of a jaundice, quite independent of the liver, caused by decreased decomposition and change of the bile in the blood. He rests, however, too much upon observations which are now known to be incorrect, those of the change of the bile acids into bile pigment.|| The late Dr. Murchison may be looked upon as one of the most prominent modern defenders of this theory, and the following account of it is taken from his work.¶

The greater part of the bile after having been poured into the intestine is taken up by the radicles of the

* Dan. Sennert, *Epitome universam doctrinam summa fide complectens*, edid. Bonetius, Col. Allob. 1655. p. 681.

† Cullen, *First Lines of the Practice of Physic*, § 1817.

‡ Portal, *Histoire de l'Académie royale des Sciences*, 1777, *Mémoires*, p. 604.

§ Gardien, *Traité complet d'accouchements*, Paris, 1816, t. iv. p. 95.

|| Frerichs, *op. cit.* Bd. i. p. 94.

¶ Murchison, *Clinical Lectures on Diseases of the Liver*, Lond. 1868. p. 375.

portal vein, and thus passes into the general mass of the blood. In health, the bile suffers a decomposition, probably an oxydation, and is cast out of the system by the lungs or kidneys. But in some diseased states, this change does not take place; and the bile circulates with the blood, causing a jaundice. The diseased states which hinder these changes of the bile from taking place are: i. The action of certain poisons on the œconomy; they are chiefly those poisons which cause an acute parenchymatous degeneration of the glands and muscles. ii. Nervous influences, as fright. iii. Bad hygienic conditions: and iv. a very great increase in the secretion of bile, so that more is poured out into the gut than can be taken up and changed in the blood into colourless material: a jaundice therefore arises from the circulation of bile pigments in the blood.

This theory rests for support chiefly on the observations of Bidder and Schmidt who found only slight traces of bile in the fæces of dogs.* But Hoppe-Seyler ten years after, found abundance of cholalic acid and undecomposed biliary acids in the fæces of dogs. He looks upon cholalic acid as a product of a fermentation or sort of digestion of the bile acids, very like the splitting up of hippuric acid into glycocoll and benzoic acid in decomposing urine.†

In the present state of knowledge it cannot be said whether the whole of the bile secreted be at once cast out of the body or not. Schiff and his followers would say that the greater part of the secretion, bile acids and bile pigment, is reabsorbed into the blood, and again excreted by the liver.‡

Granting, however, that the liver has this power of

* Bidder and Schmidt, *Die Verdauungssäfte und die Stoffwechsel*, Mitau and Leipzig, 1852, p. 217.

† Hoppe, *Arch. f. path. Anat.* 1862, Bd. xxv. p. 181; 1863, Bd. xxvi. p. 535.

‡ See p. 147 *et seqq.* for a discussion of this.

again excreting the bile, it is quite unlikely that such absorption of bile should ever become the cause of jaundice. For all the bile absorbed by the vessels is at once carried by the portal system to the liver. The liver, on the showing of Schiff*, and Tarchanoff,† would draw to itself the bile acids and bilirubin in the blood, and forthwith excrete them in the bile. Accepting Schiff's views then, it would therefore seem most likely that if any bile acids and bile pigments were absorbed by the intestine, they would again appear in the bile without entering the general circulation; and without entering the general circulation no jaundice can be brought about.

The only instance in which this theory, to my mind, can be entertained, is the case of a permanent obstruction of the circulation through the portal vein. This vessel has been artificially obliterated, and traces of the bile acids and bile pigment were found in the urine, traces, however, which soon disappeared.‡ It is known that in cases of thrombosis of the portal vein jaundice is a common symptom; but it also appears to be a permanent, and not merely a passing phænomenon.

* Schiff, *Arch. f. d. ges. Phys.* 1870, Bd. iii. p. 598; and *Giorn. di Scienze nat. ed econ.* Palermo, 1869, Vol. iv. p. 9.

† Tarchanoff, *ibid.* 1874, Bd. ix. p. 332. See also Feltz and Ritter, *Journal de l'Anat. et de la Phys.* 1870, p. 315. The experiments of Huppert (*Arch. d. Heilkunde*, 1864, p. 244) and of E. Bischoff (*Zeitschrift f. rat. Med.* 1864, Bd. xxi. p. 125) would seem in some degree to be against Schiff and Heidenhain. Huppert after injecting bile acids into the blood found only a fourth or a third excreted by the liver. What becomes of the rest? The kidneys do not excrete them. According to Bischoff, they are oxydised in the blood. This power of oxydation has, however, a limit; this limit is passed in jaundice, and bile acids appear in the urine.

‡ Schiff, *op. cit.* p. 609.

CHAPTER XI.

THE SYMPTOMS OF JAUNDICE.

THE first change from health to jaundice is seen in the colour of the conjunctiva. It becomes yellow. This is the symptom commonly first noticed by the friends of the patient, a day or two before the skin has changed its hue. In the lower orders it may often be found that the change of colour in the face is the first to draw attention, the yellowness of the eyes having been passed by. With the better classes, the eyes are commonly the first to be noticed. When the eyes show the first appearance of yellowness, however slight it may be, the urine will also give a good reaction with Gmelin's test, showing the presence of bile pigment. How soon these symptoms set in after the obstruction to the flow of bile is first set up, there are at present no very certain means of judging. It is usually said that they appear after the third day of obstruction;* but this conclusion is drawn from observations upon dogs. In these animals the conjunctiva has a brownish appearance, very unlike the pearl white of a human sclerotic, and I look upon this as a hindrance to the early detection of changes of colour. From observations upon men, I should be inclined to put the first appearance of jaundice much earlier after obstruction; perhaps within the first twenty-four or forty-eight hours. In this opinion I am supported by several clinical observers.† The serous exudations will

* Frerichs, *Klinik d. Leberkrankheiten*, Braunschweig, 1858, Bd. i. p. 99. In my own experiments upon cats, the conjunctivæ did not become discoloured for many days after the operation. (*St. Bartholomew's Hosp. Reports*, 1873, Vol. ix. p. 161.)

† Siebert, *Diagnostik d. Krankheiten des Unterleibes*, Erlangen, 1855, p. 283. Audigné (*Gaz. méd. de Paris*, 1874, in Virchow and Hirsch's *Jahresb. f.* 1874, Bd. i. p. 349) found that bile pigment could be detected in the urine in three to four hours after ligature of the common duct of a dog. As the urine of dogs so often contains in health a body which gives a reaction precisely similar to that of bile pigment, this observation can be scarcely looked upon as conclusive.

sometimes after death give a reaction with Gmelin's test when little or no trace of jaundice exists in the skin.

After the conjunctiva, the skin of the face becomes yellow. At first it may be no more than a sallow tinge, hard in some persons to tell from the natural tint of the skin. This is especially the case with persons of dark complexion. Those who are fair show the change earlier. From the face it spreads over the upper part of the trunk and thence over the belly and limbs, the legs being the last to show the yellow tint.

As a rule, the yellow colour of the skin is spread all over the body, no part being more deeply stained than the other. It is, however, not uncommon to see, in cases of slight jaundice, the upper part of the body yellow, while the belly and legs are free from unnatural colour. Frerichs has made the same observation,* and Hecker has noticed a case of acute yellow atrophy in which the upper part only of the body was coloured yellow.† But in all cases of severe jaundice which have fallen under my observation the whole of the body has been nearly equally jaundiced.

In some old authors,‡ a jaundice limited to the right half of the body and of the face and hands§ (*icterus dimidiatus*) has been described. I scarcely feel able altogether to reject these statements when an observation of a like kind has been recorded by so credible a witness as Joseph Frank. He found a lady to have at first jaundice of

* Frerichs, *op. cit.* Bd. i. p. 112.

† Hecker, *Monatsschrift f. Geburtsk.* 1863, Bd. xxi. p. 212. Cf. van Swieten, *Comment*, § 950, Lugd. Bat. 1755, t. iii. p. 141.

‡ Behrens, *Ephemerides Nat. Cur.* Noriberg. 1715, Centuria iii. obs. lxiv. p. 145. An old man, seized with right hemiplegia, had jaundice of the same side of the body as the hemiplegia: the right side of nose was yellow, the left natural in colour. Behrens quotes from Ettmüller (*op. med.* Francof. ad Moen. 1697, t. ii. p. 844) a similar case. I have been unable to verify the reference. Morgagni (*De sedibus, etc.* Ep. xi. § 14) mocks at Behrens' account.

§ Strack, *Journal de Médecine*, 1768, t. xxviii. p. 163.

the right side only, but in two weeks it spread over the whole body.* This observer surely possessed as good means of forming an opinion on this point, as anyone at the present day. The appearance must, however, be extremely uncommon, one of the rarest phenomena in medicine. Peter Frank says he has never seen such a thing, and thinks it very hard to explain;† in which every one who is able to form an opinion on the matter must agree with him. Pouzol attempts to explain it by bringing into notice the varying vascular supply of different parts of the skin, which would cause a like variation in the supply of bile pigment.‡ This may serve to explain some cases of a yellow colour in spots (*icterus variegatus*); these have, however, still to be proved to be jaundice. It does not explain the appearance of jaundice in one half of the face while the other half remains natural. Morgagni can only explain Behrens' case by supposing a slowness of the circulation in the paralysed side and thus no time being given to tinge the parts.§

The older physicians were delighted to enumerate numberless species of jaundice according to the amount of bile pigment present in the skin. Aretæus describes two species, the white and black, *melas icterus*, a word which remains in use in our own day, and says there are myriads of stages between the two.|| Many of the so-called species of jaundice are quite different diseases, *icterus albus*, *ruber*, and *cæruleus* being the names for chlorosis, erythema, and cyanosis.

The mucous membranes do not share in the yellow

* Joseph Frank, *Præceps Medicæ universa præcepta*, Lips. 1843, Part iii. Vol. ii. Sec. ii. Fasc. i. p. 278.

† Peter Frank, *De curand. hom. morb. epitome*, Vienna, 1821, Lib. vi. pars iii. p. 308.

‡ Pouzol, *Essai sur l'ictère*, Paris 1872, p. 63.

§ Morgagni, *loc. cit.*

|| Aretæus, *De causis et signis*, Adams' ed. p. 83.

tint of the skin. The lips, for example, retain the redness of health, and the inside of the mouth shows the usual colour.* A yellow colour may be seen, however, if pressure be made so as to drive all the blood out of the mucous membrane, and allow the tint which is underneath that of the blood vessels to appear. There is one part of the mucous membrane of the mouth, that under the tongue, which is often yellow, almost constantly so, an appearance noticed by Hippocrates† but to which little attention has been paid. Lonjon thinks that in every case of jaundice the *velum palati* shows a deep and constant yellow colour.‡ And Pupier says that the roof of the mouth is the first to show the yellow colour and the last to lose it.§ It is true that the roof, where the bone is thinly covered, usually does show a yellow tint.

The secretion of mucous surfaces and those of the glands which open upon mucous surfaces or the skin, saving always the notorious example of the kidneys, do not as a rule contain bile pigment. The saliva is colourless. I have often tested it in cases of severe jaundice without being able to detect any reaction with nitric acid.|| In like manner the tears, the sweat, and the milk of jaundiced patients are as colourless as in health. To this statement there are rare exceptions.

* Villeneuve (*Dict. des Sciences méd.* Paris, 1818, Vol. xxiii. p. 405) says the lips become a deep yellow, and Lonjon (*Gaz. méd. de Paris*, 1845, p. 231) that the inside of the mouth is yellow.

† Hippocrates, *De morb.* Lib. ii. Cap. xxxviii. Littré's ed. t. vii. p. 54.

‡ Lonjon, *loc. cit.* Decaisne (*Comptes rendus des Séances de l'Académie des Sciences*, 1871, t. lxxiii. p. 1486) noticed the same appearance in an epidemic of jaundice at Paris.

§ Pupier, *Gaz. hebdomadaire*, 1875, p. 307.

|| Mosler (*Berliner klin. Wochenschrift*, 1866, p. 173) could find neither bile pigments nor bile acids in the saliva of the parotid gland from three jaundiced patients. Dr. Samuel Fenwick, indeed, (*Lancet*, 1877, vol. ii. p. 303) says that he has examined the saliva in a large number of cases of jaundice, and, whenever the disease has been recent, that he has found the pigment on evaporation. Nothing is said about any chemical means having been used for the recognition of the pigment, so that the presence of biliary pigment in the specimens examined remains doubtful.

The sweat is the most common exception.* The linen near the armpits may often be seen stained yellow as if wetted with the urine. This is certainly the most common place for the sweat to be coloured, although the appearance of colour in other parts has been recorded. Thus in an old case of Chomel's, in a woman subject to epilepsy, jaundice came on; a thick sweat broke out during the fit, and the linen with which they wiped the patient was tinged of a saffron colour.† Sir Henry Marsh says that Cheyne had met with a patient whose handkerchief was stained yellow when she wiped her face.‡ Andral mentions a really curious case in which the stools were white, but the skin and conjunctiva colourless; nevertheless the urine was bilious and the linen used to wipe the sweat off the head was coloured yellow. After death the liver was found softened, not fatty; the cystic and hepatic ducts free from bile and a colourless serous fluid in the gall bladder; nothing unnatural was found in the duodenum.§ Textural changes, like those in the kidneys, do not appear in the sweat glands. Frerichs figures brownish granules within the glands, but nothing like the great masses of pigment seen in the kidney.||

There are some early notices of a change of colour of the saliva in jaundice,¶ and one of the best of these we owe to so excellent an observer as John Huxham. A gentleman 40 years old, jaundiced, took overnight, with some other medicines, gr. viii. of calomel. The next day a very green saliva poured out of the man's

* Noticed by Galen, *De sanitate tuenda*, Lib. iv. Cap. iv. Kühn's ed. Lipsiæ, 1823, vol. vi. p. 250. It is, however, only said that the sweat is bitter.

† Chomel, *Histoire de l'Académie royale des Sciences*, Année 1737, Paris, 1740, p. 49.

‡ Henry Marsh, *Dublin Hospital Reports*, 1822, Vol. iii. p. 269.

§ Andral, *Clinique méd.* Paris, 1839, 4e éd. t. ii. p. 374. Cf. p. 320.

|| Frerichs, *Path.-anat. Atlas zur Klinik der Leberkrankheiten*, Tafel i. Fig. 6.

¶ Nuck, *Sialographia*, Lugd. Batav. 1690. p. 49. Riedlinus, *Lineæ Medicæ*, August. Vindelic. Anni 1697. p. 88.

mouth, exactly like green bile, but thinner. This flow of green saliva lasted 40 hours, and very nearly equalled two quarts in amount. The green colour of the saliva passed into yellow, which lasted another 40 hours and then the salivation disappeared as suddenly as it came on. Huxham does not think it due to the mercury, on account of the smallness of the dose; the patient had before been salivated, apparently without mercury.* But the observer who has paid the most attention to the saliva, whether in health or disease, is undoubtedly Samuel Wright; and he has published the most complete account known of the saliva in jaundice. He says that in jaundice, the saliva is seen in two forms, colourless and coloured, and that the coloured bilious saliva is of various shades, from a golden yellow to a deep olive; it is always abundant, and though it sometimes alternates with that of other secretions, it rarely permanently diminishes until the patient be free from the jaundiced tinge. The salivary glands are usually tinged and of a dull red colour, but they are not painful and they show no signs of active inflammation.† Wright thinks a discharge of bilious saliva may precede, accompany, or even hinder, an attack of jaundice. He gives three cases of coloured saliva, in all of which salivation was present; and in the two first mercury was given; in the third the treatment was by "salines and aperients." The saliva tasted bitter to the patients themselves. Dr. Budd likewise speaks of a case of jaundice in which salivation was caused by mercury, and the saliva was deeply coloured with bile.‡ Since, however, the custom of giving mercury for jaundice has fallen out of use, such cases seem to be less common. Leyden, giving two grains of calomel every three hours,

* Huxham, *Phil. Trans.* 1724. Vol. xxxiii. p. 63.

† Wright, *Lancet*, 1842-43. Vol. i. p. 559.

‡ George Budd, *On Diseases of the Liver*, London, 1857. Third Ed. p. 469.

caused a salivation; and with the salivation a distinct yellow appearance of the saliva.*

The records of a bilious saliva without salivation are rare, a yellow appearance of the buccal mucus being always excepted.† There is, indeed, a case of Dr. Hilton Fagge's, in which the saliva just before death had the colour of bile. The patient, a woman, had for six months suffered from a macular syphilide, and for three months from jaundice; she denied having used mercury; but during the 10 days of her stay in Guy's Hospital she had the $\frac{1}{16}$ gr. of perchloride of mercury given three times a day, and on the day before death three grains of calomel. It does not appear that there was any notable salivation.§ Gubler also shortly mentions a case of syphilis and jaundice in which the saliva was yellow; he does not say that the patient was salivated.§

The milk of women suckling sometimes contains bile pigment. This was first proved by means of chemical tests by Gorup-Besanez.|| Older cases of a yellow appearance of the milk in jaundice have likewise been recorded.¶ Hervieux found quite lately, in an epidemic jaundice in the *Maternité* at Paris, that in all the women who were suckling, the milk was coloured yellow.

* Leyden, *Beiträge zur Pathologie des Icterus*. Berlin, 1866. p. 208.

† Andral, *Clinique méd.* Paris, 1839. 4e Édition, t. ii. p. 320.

‡ Hilton Fagge, *Trans. of the Path. Soc. of London*, 1867. Vol. xviii. p. 136.

§ Gubler, *Gaz. méd. de Paris*, 1854, p. 215.

|| Gorup-Besanez, *Arch. f. phys. Heilkunde*, 1849. Jahrg. viii. p. 719.

¶ Peter Frank, *De curandis hominum morbis*, Vienna, 1821. Lib. vi. pars iii. p. 305. The vaginal secretion was likewise coloured.

Henry Marsh, *Dublin Hospital Reports*, 1822. Vol. iii. p. 263.

Bright, *Guy's Hospital Reports*, 1836. Vol. i. p. 623.

Wunderlich, *Arch. d. Heilkunde*, 1860. Jahrg. i. p. 35.

Marsh's, Bright's, and Wunderlich's cases are from observations on the mammary gland after death. There are some other cases sometimes set down as instances of bile being present in the milk, which merely show that the milk had from some cause or other a bitter taste. (Ol. Borrichius, in Bartholini *Acta med. Hafniensia*, 1673. Vol. ii. p. 164. Obs. lxii. and *Samml. aus. Abh.* 1792. Bd. xv. p. 121. Note.)

low.* Underwood says that he has met with some striking instances in which women, suckling and jaundiced, have communicated the disease to their offspring, which has not been cured until the child was weaned or the nurse recovered.†

I have never been so fortunate as to see the milk coloured in jaundice. A patient of mine, suckling, who had symptoms of simple jaundice, told me that the milk was coloured green. Yet on some being pressed out of the nipple, no colour was apparent; neither on applying Gmelin's test, could any certain reaction be seen; the layer of milk above the nitric acid became of a dirty yellow, markedly different from the white of the milk, but no play of colours or distinct green was seen. Nor did a green colour develope in the milk after it was kept three days.

As to the other secretions they seem to be very rarely coloured. Heberden is commonly quoted as an authority for the statement that the tears sometimes become yellow; all, however, that he does say is that one man assured him his tears were tinged in a jaundice.‡ Some French writers speak of the tears in the jaundice of the new-born being coloured; but I think this must be a mistake, the pus of an ophthalmia being coloured yellow and thus thought to be tears.§

Sander says that the nurse attending one of his cases which died of acute yellow atrophy, reported that the tears were yellow.|| This suffers the same want of proof as Heberden's case, as the doctor himself did not see the tears.

The mucus of the nose has been seen to be yellow by

* Hervieux, *Union méd.* 1872. t. xiii. p. 610.

† Underwood, *A Treatise on the Diseases of Children*, Lond. 1805. Fifth edit. vol. i. p. 27.

‡ Heberden, *Commentaries*, Lond. 1806. 3rd ed. p. 247.

§ Billard, *Traité des maladies des enfans nouveau-nés*, Paris, 1828. p. 646.

|| Sander, *Deutsche Klinik*, 1860. Bd. xii. p. 33.

one or two observers ;* Joseph Frank says he has seen the secretion of the ears altogether suppressed in jaundice.† It is likewise asserted that the vaginal mucus is sometimes coloured.‡ Bouisson says he has found the semen in the *vesiculæ seminales* manifestly yellow.§

The fluids poured into the intestinal tract are likewise devoid of colour in jaundice ; otherwise the fæces themselves would be coloured. I am not acquainted with any well authenticated case in which these fluids were coloured ; indeed it would be hard to prove the presence of bile pigment in them, apart from the fæces.|| Osborne speaks of colourless fæces floating in a bilious fluid,¶ but this seems to me best explained by supposing an admixture of urine.

Although the mucous secretions remain uncoloured in jaundice while the mucous membranes and glands remain healthy, yet the secretions may become coloured in disease. This has been already noticed in the case of the saliva. Simple catarrh does not seem to beget much change ; but the croupous exudations are very liable to be coloured in jaundice. For example, in simple catarrh of the bronchial tubes, the mucus is rarely coloured, although I have met with such an instance in one case ; yet in pneumonia complicated with jaundice, where a croupous exudation takes place, the sputa are very commonly coloured.

* Kercksig, Hufeland's *Journal*, 1799. Bd. vii. Stück iii. p. 98. There is also an old case by Riedlinus, *Lineæ med. anni 1697*. August. Vindel. p. 88.

† Joseph Frank, *op. cit.* p. 282.

‡ Peter Frank, *De curand. hom. morb.* Viennæ, 1821. Lib. vi. Pars iii. p. 305.

Reclus, *Gaz. des Hôp.* 1872. p. 259.

Stokes, *Lond. Med. and Surg. Journal*, 1834. vol. v. p. 199.

§ Bouisson, *De la bile*, Montpellier, 1843. p. 151. A similar instance is quoted by Joseph Frank (*op. cit.* p. 281.) from Petermann (*Obs. Med.* Dec. 1. No. 9.)

|| Bouisson (*de la Bile*, Montp. 1843, p. 150) says that Voigtel (*Handb. d. path. Anat.* Halle, 1804, Bd. i. p. 552) records a case in which the pancreatic fluid was yellow in jaundice. What Voigtel does say is that a yellow fluid was found in the pancreas of a jaundiced person.

¶ Osborne, *Dublin Quarterly Journal*, 1853, vol. xv. p. 106.

The fluid exudations into the serous cavities are among the first to show the presence of bile pigment.

The extra-vascular tissues are not coloured in jaundice. There are old stories quoted of the hairs sometimes changing colour; which on examination do not bear out the purpose for which they are brought forward: the case quoted by Schenck suggests chlorosis rather than jaundice;* and Riedlinus'† is simply that a jaundiced woman told him that whenever she pulled out a hair, a yellow drop appeared at the spot whence the hair came out.‡ Stokes, however, tells us that one of his friends considered that the hairs were unquestionably coloured in some cases of jaundice. It does not seem that Stokes had ever seen such cases.‡ Neither have I.

Huxham's statement that the teeth were coloured green for a fortnight after convalescence in his case of bilious saliva§ is confirmed by Wright, who says that in like cases he has seen the teeth coloured permanently yellow, green, brown, or black according to the amount of bile present in the saliva.|| Thomas Bell says he has seen more than one example of the injection of a tooth with bile in cases of jaundice.¶ It would seem from Bell's statement that only one tooth was coloured among many. The rule in jaundice is that the teeth look uncommonly white from contrast to the surrounding coloured tissue, as the teeth of a negro do.

There is a curious case mentioned by Bleicher, of a man aged 40 who on the 8th day of a jaundice with fever, passed blue urine; and at the same time the

* Schenck, *Obs. med.* Lib. iii. de ictero, Obs. i. Lugduni, 1644, p. 405. Quoted from Cornelius Gemma, *Comoscrit.* lib. i. cap. 7.

† Riedlinus, *Lineæ med.* Anni 1697, August. Vindel. p. 88.

‡ Stokes, *Lond. Med. and Surg. Journal*, 1834, vol. v. p. 199.

§ Huxham, *Phil. Trans.* 1724, vol. xxxiii. p. 64.

|| Wright, *Lancet*, 1842-43, vol. i. p. 562.

¶ Thomas Bell, *John Hunter's Works*, Palmer's ed. London, 1835, vol. ii. p. 19, note.

lips, tongue, and teeth, became blue. Eight days after he was cured.*

Pain is not a complication of jaundice. Jaundice caused solely by the pressure of a tumour upon the hepatic ducts, or by a plug of mucus within them, is not accompanied by any pain due to the jaundice; if pain be present it is due to some other complication of the disease. It is, however, otherwise when the jaundice is due to the passage of a rough angular gall stone down the ducts; the friction and forcible dilatation of the ducts sometimes cause agony so great that it is needful to give the patient chloroform to remove the pain.

Pouzol, speaking of the slight troubles and absence of pain which in general accompany jaundice, says that he has noticed a headache sometimes attend this disease: the headache is frontal or general, sometimes lancinating, sometimes giving a feeling of weight.† This is probably bilious in origin.

Patients with jaundice appear to me to be drowsier than others. They often sleep much during the day. Sleeplessness, unless due to the itching, is not at all a common symptom, although spoken of as one.‡

Heberden speaks of hiccup being seen in jaundice, but without denoting any present or future mischief.§

Symptoms of disordered digestion are seen in cases of jaundice complicated with signs of gastric catarrh; that is, a large proportion of cases. But in many cases of chronic jaundice, digestion seems to suffer but little. The appetite is good and the tongue remains clean. Frerichs states that the patients suffer from much flatulence, due to the want of bile in the intestine.|| Curiously enough, Hippocrates says pre-

* Bleicher, Schmidt's *Jahrb.* 1839, Bd. xxi. p. 48.

† Pouzol, *Essai sur l'ictère*, Paris, 1872, p. 78. Portal (*Maladies du foie*, Paris, 1813, p. 133) says shortly that heat and weight of the head are often seen in jaundice.

‡ Pouzol, *loc. cit.*

§ Heberden, *Commentaries*, Lond. 1806. Third ed. p. 246.

|| Frerichs, *op. cit.* Bd. i. p. 118.

cisely the reverse, that the jaundiced are not at all flatulent;* and in my experience of chronic jaundice it has not been at all a prominent symptom. There seems to be a dislike to fat. Those who in health have eaten and liked fat, when jaundiced, refuse it. Budd describes a patient who had, at times, a voracious appetite, with a craving for oysters and small shell-fish, which even in large quantities, never disagreed.†

The blood early suffers in jaundice. Saunders showed that, within two hours after ligature of the bile duct, the blood gave evidence of the presence of bile pigment.‡ I have repeated this experiment, following Saunders' directions exactly, but without attaining his results.‡ Frerichs in like manner, could only detect bile pigment in the blood at the end of 48 hours after the ligature of the ducts.§ I quite agree, however, with his statement that bile pigment may be found after death in the serous effusions of the chest or belly in cases where none can be detected in the urine, or any change of colour seen in the skin. I have several times verified this statement, taking care to use only the fluids from the chest, as it may be objected to those from the belly that the bile in the gall bladder may have transuded after death.

It is granted by all that the bile pigments exist in the blood in jaundice.|| The same cannot be said of the bile acids. For many years a fruitless search was

* Hippocrates, *Aphorisms*, Section v. § 72. Littré's ed. t. iv. p. 562. Οἱ ἰκτερίωδεις οὐ πᾶν τι πνευματώδεις εἰσιν.

† Budd, *On Diseases of the Liver*, London, 1857, third ed. p. 219.

‡ Saunders, *A Treatise on the Structure, Economy, and Diseases of the Liver*, London, 1803, 3rd ed. p. 111.

‡ Wickham Legg, *St. Bartholomew's Hospital Reports*, 1873, vol. ix. p. 176.

§ Frerichs, *op. cit.* Bd. i. p. 99.

|| See Lecanu, *Transactions méd.* 1831, t. vi. p. 113, note, for the bibliography of the older researches into the presence of the colouring matter of the bile in the blood. I have looked through these references, but the authors do not communicate any important results. Kane (*Dublin Journal*, 1833, vol. ii. p. 346) confirms Lecanu's statements.

made for them, only one chemist* since Pettenkofer's discovery, and that not in cases of disease of the liver, being able to find their peculiar reaction in the blood. In 1858 came Hoppe-Seyler's discovery of the bile acids in the urine† and Kühne soon after found them in the blood of jaundiced dogs, even so soon as 24 hours after complete occlusion to the ducts.‡

Huppert found them in the blood of a rabbit who lived only six and a half hours after the bile ducts were tied, and in the blood of a cat who lived more than sixteen hours after.§ Also in the blood of a man who died of acute yellow atrophy. But Ernst Bischoff could not find them in the blood, muscles, brain, or cerebro-spinal fluid of a patient who died with intense jaundice from cancer of the liver.||

When it was the custom to make analyses of the blood in mass, analyses to which little regard is now paid, several examinations of the blood from jaundiced persons were made. Lecanu¶ and Simon** found the amount of colouring matter of the corpuscles decreased, while Denis†† found the globules natural in amount, but the albumen decreased. Gorup-Besanez‡‡ found an increase of the water, and decrease of the blood-corpuscles; and, at the same time no increase of fatty matters, and no cholestearin. The absence of any increase of fat or cholestearin was noticed also

* C. G. Lehmann, *Lehrb. d. phys. Chem.* Leipzig, 1853, 2te Aufl. Bd. i. p. 122. Jac. Moleschott (*Zeitschrift f. rat. Med.* 1847, Bd. vi. p. 387) thought he detected bilin, i.e. the bile acids in the blood in a case of "hepatitis."

† For history of this, see the section on the urine.

‡ Kühne, *Arch. f. path. Anat.* 1858, Bd. xiv. p. 347.

§ H. Huppert, *Arch. d. Heilk.* 1864. Jahrg. v. p. 253.

|| Ernst Bischoff, *Zeitschrift f. rat. Med.* 1864, iii. Reihe, Bd. xxi. p. 142.

¶ Lecanu, *Trans. méd.* 1831, t. vi. p. 109. The blood which he examined did not clot till long after it had cooled.

** Simon, *Animal Chemistry*, Day's Trans. 1845, vol. i. p. 330.

†† Denis, *Essai sur l'application de la Chimie à l'étude physiologique du Sang*, Paris 1838, p. 309.

‡‡ Gorup-Besanez, *Arch. f. phys. Heilk.* 1849, Bd. viii. p. 530.

by Kane* and Simon†. On the other hand Becquerel and Rodier found an increase in the fatty matters and cholestearin;‡ Frerichs, a large increase in the fatty matters, which were rich in cholestearin, and which rose sometimes to 4 or 5 *per cent.* Leucin was also found in the blood.§

Dr. Samuel West found, "in a case of severe jaundice, probably depending on gall stones, the patient being in a state of the most extreme anæmia, and so weak that the least exertion caused fainting," that the blood showed the following characters: "The cells were considerably diminished in number, and the blood very watery. The red cells did not form rouleaux, were much diminished in size, hardly half as large as a healthy red cell, most irregular in shape, and deeply coloured, resembling the bodies described by Lebert as tubercle corpuscles. The white cells were in relative excess. In this one particular only did the blood in the case differ from that described in idiopathic or pernicious anæmia. The patient, however, recovered, and with his improvement, his blood gradually returned to its normal condition; and on his leaving the Hospital this note is recorded: Red blood cells nearly natural again; here and there one still misshapen. They form rouleaux; the white are no longer in excess."||

Budd, though he seems to have made no analyses, says that, after jaundice has lasted some time, the globules of the blood are always less in proportion than in health. This probably results, not so much from the mere presence of the principles of the bile in the blood as from a diminution of those reparative changes which

* Kane, *Dublin Journal*, 1833, vol. ii. p. 346.

† Simon, *loc cit.*

‡ Becquerel and Rodier, *Recherches sur la composition du Sang*, Paris, 1844. p. 106.

§ Frerichs, *op. cit.* Bd. i. p. 103.

|| Samuel West, *St. Bartholomew's Hospital Reports*, 1877, vol. xiii. p. 218.

the blood naturally undergoes in its passage through the liver, and to the impaired digestion which results from the absence of bile in the bowel.* Leyden seems to incline to believe that the poverty of the blood is due to the action of the bile acids upon the corpuscles.† For my own part, I feel disposed to agree with Budd and attribute the state of the blood to the impaired action of the liver and the impaired nutrition rather than to the solvent action of the bile acids upon the corpuscles.

The fæces in jaundice are often entirely wanting in colour.‡ They have a grey or clay coloured appearance, and are less consistent than the stools seem in health. Frerichs, however, says that the stools are firmer and more consistent.§ To this statement, I fear, I cannot assent; or to that, that constipation is the rule. In simple jaundice, which is, I suppose, the most common of all kinds of jaundice, diarrhœa is very often seen. In chronic jaundice, diarrhœa is less common. In this statement I am supported by no less profound an observer than Heberden; who, granting that costiveness might be looked for in jaundice, as the irritation from the bile is wanting, says that in fact icteric persons are often disposed to have a purging. He looks upon the diarrhœa as a help to distinguish jaundice from ileus.||

Sometimes the fæces are particoloured; some part being more deeply stained with bile than the other; or even one part free from bile altogether, while the

* Budd, *On Diseases of the Liver*, London, 1857, 3rd ed. p. 468.

† Leyden, *Beiträge zur Pathologie des Icterus*, Berlin, 1866, p. 117.

‡ Hippocrates describes the stools as yellow-white and stinking. (*De morb. int.* Cap. xxxv. Littré's ed. t. vii. p. 252.) Aretæus says that their want of colour is due to absence of bile. (*On the Causes and Symptoms of Chronic Diseases*, Book 1. Chapt. xv. Adams' transl. p. 324.)

§ Frerichs, *op. cit.* Bd. i. p. 119.

|| Heberden, *Commentaries*, Lond. 1806. Third ed. p. 246. The same opinion is expressed by Powell. (*Observations on the Bile and its diseases*, London, 1800, p. 85.)

other is coloured. Graves explains this appearance by supposing that the liver secretes bile during a certain part of the digestive process, then stops, and then secretes again.* It is rare in jaundice for the fæces to be unchanged in colour, or to show more staining with bile than natural. This last has given rise to theories of polycholia, or an excess of bile, as a cause of jaundice; and is one of the points relied upon by the defenders of the theory of hæmatogenous jaundice. Doubtless the appearance of highly coloured fæces is sometimes hard to explain upon the theory of an obstruction to the duct if the admixture of foreign colouring matters, such as blood or drugs, can be disproved. Still it is well to keep in mind the facts disclosed by morbid anatomy: some of the small ducts may be obstructed high up in the liver, while the large ducts and branches leading into them are quite free; also the small amount of colouring matter that need be in the blood to bring about the appearance of jaundice.

If the fæces be colourless, there can be little doubt that no bile enters the intestine; in other words, that the obstruction of the bile duct is complete. But the contrary does not hold good. The fæces may owe their colour to other sources than the bile; as the administration of drugs, like charcoal, bismuth, or iron. Likewise the appearance of hæmorrhages into the intestinal tract in jaundice is far from uncommon, and blood mixed with the stools may readily give the deceptive appearance of a dark or brown colour to the fæces. I cannot, however, agree with Osborne that it is possible that the secretions from the bowels may be coloured while the fæces are white. He says that the fæces in jaundice may be seen to be of a white colour like putty, surrounded by a green or yellow liquid.† This seems to

* Graves, *Clinical Lectures on the Practice of Medicine*, Dublin, 1864, p. 342. Reprint of second ed. edited by Neligan.

† Osborne, *Dublin Quarterly Journal*, 1853, vol. xv. p. 106.

me to be due possibly to some error of observation. The fæces may not unfrequently be seen surrounded by a coloured liquid, but this is in cases where the bilious urine has been suffered to mix with the uncoloured stools, and thus a deceptive appearance caused.

The fæces in jaundice do not seem to have been examined with much attention by the chemists.* Dr. Austin Flint, the younger, has found that they contain no stercorin,† a substance, which he says, is derived from the decomposition of cholestearin, and which always appears in natural fæces. Dr. Flint thinks that no cholestearin is found in natural fæces. Hoppe-Seyler commenting on Dr. Flint's researches says that stercorin is nothing more than an impure cholestearin; cholestearin itself being abundantly found in the fæces of mammalia, including man.‡ A large amount of fat was also found by Dr. Flint in the fæces of jaundice: Farines, in an old analysis, found the greater part of the fæces in jaundice to be formed of a fatty matter, soluble in æther.§ A like result was attained by Trommer, who analysed the fæces of one medical student who was jaundiced, and compared the results with those obtained from the fæces of another medical student, who was healthy, but ate the same food. Far more fat was found in the fæces of the former than of the latter.|| Jaundiced persons, it is well known, dislike fat.

The Urine. The urine very early shows changes in jaundice. It becomes highly coloured.¶ Linen or

* See Hoppe-Seyler, *Phys. Chemie*, Berlin, 1878, p. 358.

† Austin Flint, *Recherches exp. sur une nouvelle fonction du foie*, Paris, 1868, p. 101; also in *American Journal of the Medical Sciences*, 1862, vol. xlv. pp. 358 and 364.

‡ Hoppe-Seyler, *Virchow's Jahresbericht f.* 1868, Bd. i. p. 97.

§ Farines, in Orfila, *Elém. de chimie appliquée à la méd. et aux arts*, Paris, 1836, t. iii. (Quoted by Bouisson, *de la Bile*, Montpellier, 1843, p. 151.)

|| Trommer, reported by F. von Niemeyer, *Text Book of Practical Medicine*, trans. by Humphreys and Hackley, New York, 1870, Vol. i. p. 679.

¶ The change in colour was noticed by Hippocrates (*De aff. int.* Cap. xxxv. Littré's ed. t. vii. p. 252 et seqq.)

white paper dipped into it is stained yellow. This is an appearance often noticed by the patients themselves. The froth on the surface shows a yellow look and is long in disappearing.

The colour may be scarcely darker than natural, and need a chemical test to show the presence of bile: or the urine may be almost as dark as porter, of a green brown, or brown black. The reaction is acid, and the specific gravity is not low, seldom falling below 1010.* The urine is commonly clear; but may sometimes be turbid owing to the presence of urates, apparently not dependent upon the temperature of the patient.

The quantity of urine passed in the 24 hours in jaundice is subject to considerable variations. Becquerel found in three cases in which he carefully noted the appearances of the urine that in the first, a man, the amount in 24 hours was 1419.C.C.; in the second, a man jaundiced after a violent dispute, it was 634.C.C. and in a third, a pregnant woman, it was 640.C.C.† The observations, however, were only made on one day, and are therefore less valuable than those which follow and which were made in succession. Leyden found in one of his cases that the urine was increased in quantity while the temperature was normal, but sank in amount during a paroxysm of fever.‡ A. Vogel found in his case of jaundice lasting for many months, and due to cancer of the liver, that the amount of the urine varied from 1350.C.C. to 2000.C.C.§ Kölliker and Müller in their observations on a woman of 25, suffering from simple jaundice found that the mean amount of the urine dur-

* Gorup-Besanez (*Arch. f. phys. Heilkunde*, 1849, Jahrg. viii. p. 713) says that the specific gravity of the urine of jaundice is commonly high, about 1031.

† Becquerel, *Séméiotique des Urines*, Paris, 1841, pp. 413 and 393.

‡ Leyden, *Beiträge zur Path. des Icterus*, Berlin, 1866, p. 205. He likewise gives cases of increased or abundant flow of urine at pp. 114 and 184, although in the former of these two the temperature was high.

§ A. Vogel, *Zeitschrift f. rat. Med.* 1854, Bd. iv. (neue Folge) p. 391.

ing the jaundice was 1670.C.C.; during the convalescence 1401.C.C.; when quite well 1370.C.C.* So that in this case there seems some evidence that the amount of urine passed was really increased in amount.

Julius Jacobs found the amount in three cases to be 2409.C.C. 1638.C.C. and 1332.C.C.†

In four cases examined by Valmont the amount was found rarely to rise above 1000 C.C. One of these was believed to be a case of cancer of the liver; in the other three, cirrhosis was diagnosticated; and in two, verified after death.‡

I have measured the amount of urine passed in the 24. hours in ten cases of jaundice due to various causes. The highest mean was in a case of complete obstruction to the ducts by a hydatid cyst, and equalled 2790 C.C. in the twenty-four hours. The lowest mean was in a case of cancer of the pancreas and liver and equalled 570. C.C. In two other cases of jaundice due to the same cause the mean were 1971. and 1120. C.C. In the remaining six cases the means of the urine passed were 1100, 1355, 1433, 1481, 1788, and 2234. C.C. amounts not above or below the standard of health§

In some cases of jaundice it has been noticed that, as the patient was dying, the amount of urine passed become very small, or indeed sank almost to nothing. Such a case has been noticed by Devay in which the

* Kölliker und Müller, *Verhandlungen der phys. med. Gesellschaft in Würzburg*, 1856, Bd. vi. p. 497.

† Julius Jacobs, *Arch. f. path. Anat.* 1877, Bd. lxi. p. 487.

‡ Valmont, *Étude sur les causes des variations de l'urée dans quelques maladies du foie*, Thèse de Paris, 1879, p. 36 et seqq. See also Vulpian, *Clinique méd. de l'Hôpital de la Charité*, Paris, 1879, p. 253.

§ Wickham Legg, *Med. Chir. Trans.* 1876, Vol. lix. p. 149. Dogs, whose bile ducts have been tied, pass a greatly increased quantity of urine. Tiedemann and Gmelin (*Recherches expérimentales sur la digestion*, Paris, 1827, Partie ii. p. 47) also noted that the urine was abundant. Feltz and Ritter found that after the injection of bilirubin into the veins, the amount of urine was much increased. (Robin's *Journal de l'Anat. et de la Phys.* 1875, t. xi. p. 155.

urine was suppressed three days before death after a 7. years' jaundice from gall stones.*

Albumen is rarely absent from jaundiced urine. The amount is indeed small, and some care is needed to detect it. No cloudiness is given by heat, as a rule; but opalescence, however, appears on dropping a little nitric acid into the boiling urine. I look upon this as evidence of the presence of albumen in the urine. No white ring is commonly formed where a layer of nitric acid touches the urine.

According to Kühne, the cause of the presence of this small quantity of albumen in jaundiced urine would be due to the action of the bile acids upon the red corpuscles.† It is well known that the red corpuscles, wherever they come in contact with the bile acids, are dissolved. Free hæmoglobin thus becomes present in the plasma of the blood, and is thrown out by the kidneys. The bile acids must be present in but small quantity in the blood, or a much larger amount of albumen would be thrown out by the kidneys.

Sugar is not often met with in jaundiced urine. Indeed though I have carefully looked for it in nearly all the cases which I have examined, I have never met with it. The test which I have used has been Trommer's. On theoretical grounds the appearance of sugar should be rare, as one important form of diabetes does seem to arise from the liver. I have shown that after ligature of the bile duct glycogen disappears in the liver, and that when the fourth ventricle is irritated under the same circumstances, no sugar appears in the urine.‡ So in jaundice if the obstruction to the ducts be complete, no sugar from the liver should appear in the urine. There are, however, a few cases

* Devay, *Gaz. méd. de Paris*, 1843, p. 263, Cf. Frerichs, *op. cit.* Bd. i. p. 147.

† Kühne, *Lehrb. d. phys. Chemie*, Leipzig, 1868, p. 545.

‡ Wickham Legg, *St. Bartholomew's Hospital Reports*, 1873, Vol. ix. p. 161, and *Arch. f. exp. Path.* 1874, Bd. ii. p. 384.

in which sugar has appeared in the urine of jaundice. In Golowin's case, a dog was artificially jaundiced, and each time that milk was given to the animal, sugar appeared in the urine.*

Valmont has, however, given 150 or 200 grammes of *sirop de glucose* to patients suffering from jaundice, and not been able to detect any sugar in the urine passed afterwards.† In some cases of an advanced cachexia, he says that he found the sugar again, but with large doses it is possible to cause glycosuria even in healthy people.

There is an important case of diabetes recorded by Dr. Bright, in his paper on diseases of the pancreas. A man, 49 years of age, first felt symptoms of diabetes in the month of March. In the beginning of September he began to be jaundiced; and at the end of December, the sugar had disappeared from the urine. The man died on March 1st, and the common duct was found to end in a *cul de sac* in the diseased substance of the pancreas, complete obstruction having taken place.‡ The theory of this case would be that the gradual obstruction of the ducts caused the liver to cease its glycogenetic function, and the diabetes also to end: while at last the patient died from the effects of the jaundice.

Frerichs has reported the following case. After death the head of the pancreas was found enlarged and completely obstructing the ducts. Old capillary apoplexies were found in the *pons Varolii*. The man was 50 years old and began to be yellow in December. No suspicion of diabetes seems to have been aroused until about March 15th, when it was discovered that the patient was passing sugar. The

* Golowin, *Arch. f. path. Anat.* 1871, Bd. liii. p. 428.

† Valmont, *Étude sur les causes des variations de l'urée dans quelques maladies du foie*, Thèse de Paris, 1879, pp. 24, et seqq.

‡ Bright, *Med. Chir. Trans.* 1833, Vol. xviii. p. 3.

quantity was never more than 5000 C.C. in the 24 hours and the specific gravity varied from 1009 to 1018. The amount of sugar was estimated by Soleil's polarisation apparatus, and varied from .822 to 2.88 *per cent.* Three days before death the sugar disappeared from the urine, and after death none could be found in the substance of the liver.* Dr. George Harley says that on two occasions he found a little sugar in the urine of a jaundiced man,† but he does not give his method of testing.

It is a matter of doubt among physiological chemists whether the bile pigments be not natural constituents of the urine. It is acknowledged generally that they may be found in the urine of healthy men in summer weather, after much drink, long-fasting, &c. In the urine of many animals, such as dogs and cats, there is a substance almost always present which closely imitates the reaction of bile pigment with nitric acid.

The best way of testing for bile pigment in the urine is as follows: ordinary nitric acid, in which some nitrous acid is nearly always present, is poured into a test tube for the depth of an inch. On to the surface of this the urine to be tested is gently poured by means of a pipette, down the side of the tube, so that the two fluids may touch, but not mix. A red line forms at the place of contact in every urine. If the urine contain bile pigment, however, a zone above becomes green, then blue, violet, and lastly red, the uppermost ring being green. This colour is certainly the most characteristic, and without it, the reaction must always be thought dubious. In most bilious urines only the green colour is seen. The varying shades of colour answer to the stages of oxydation of the bile pigment. The reaction is known by the name of Gmelin.

Fleischl says that it is now common to practice Gme-

* Frerichs, *op. cit.* Bd. i. p. 153.

† George Harley, *Jaundice*, London, 1863, pp. 78 and 79.

lin's reaction according to a modification of Brücke's.* To pure nitric acid, obtained by boiling, concentrated sulphuric acid is cautiously added. The sulphuric acid from its great specific gravity falls to the bottom. It hinders the too rapid developement of the colours, and the reaction gradually spreads upwards from the line of union of the two fluids, instead of taking place simultaneously throughout the liquid; all the different colours may be seen one above the other. Instead of pure nitric acid, a solution of nitrate of sodium may be used.†

Carefully practised, it is by far the best test for bile pigment.‡ Other methods have been proposed, as that of Maréchal, who mixes two or three drops of tincture of iodine with the urine, and finds an emerald green colour given to the fluid.§ This test, however, is lacking in delicacy. It is hard to perceive the green colour when the amount of bile pigment is small, though easy to find when the colour of the urine is so deep as not to be mistaken for anything else but bilious urine. At the beginning and end of an attack of jaundice the iodine often fails when the nitric acid gives a distinct green. Dr. Walter Smith, however, thinks it a delicate reaction.||

Another test for the presence of bile pigment has been lately brought forward, *violet de Paris*, or methylanilin violet. It appears, however, that the reaction seen equally well with urine coloured with senna or rhubarb, or by the carbolic acid treatment. It is thus

* Brücke, *Sitzungsberichte d. math.-naturw. Classe d. k. Akad. d. W. Wien*, 1859, Bd. xxxv. p. 14. Brücke himself advises dilute nitric acid.

† Fleischl, *Chem. Centralblatt*, 1875, p. 568 from the *Journal of Chemical Society*.

‡ Rosenbach (*Centralblatt f. d. med. Wissenschaften*, 1876, p. 5) proposes a modification of Gmelin's test. Some of the urine is filtered through filtering paper and then a drop of nitric acid let fall on the paper as it lies in the funnel. A fine green circle is developed.

§ Maréchal, *Journal de Pharmacie et de Chimie*, 1869, 4e Série, t. ix. p. 189.

||-Walter G. Smith, *Dublin Journal of Medical Science*, 1876, Vol. lxii. p. 449.

worthless for the purpose for which it has been introduced.*

Ultzmann also recommends the following method: 10 C.C. of the urine are mixed with 3 or 4 C.C. of a 33 *per cent.* of caustic potash solution. The mixture is then acidified with pure hydrochloric acid: a beautiful emerald green colour is seen if bile pigment be present.†

Städeler believes that the chief pigment in jaundiced urine is biliprasin; because the urine becomes green with acids and brown with alkalies, and solutions of biliprasin show like reactions.‡ On the other hand, Schwanda, from numerous observations, asserts that bilirubin is the chief pigment in jaundiced urine, and that only traces of biliprasin can be found, so that it is the bilirubin which is the chief cause of colour, not biliprasin.§ Städeler's test is not nearly so delicate as Gmelin's. It is useful sometimes in determining if the high colour of the urine be due solely to drugs. Rhubarb and santonin both give a high colour to the urine, hardly to be distinguished by the eye from that of jaundice. Alkalies, however, deepen to a red the urine passed after rhubarb and santonin, but give a brown colour to the urine of jaundice.

Schwanda has attempted the estimation of the bilirubin passed in the urine, and if his results may be trusted, the amount is extremely small, even in cases where the urine is deeply coloured. The greatest amount found was .015 grm. in the 24 hours. In one case it was as little as .002 grm.|| Thus the largest amount which the urine contained was one part of bile

* Gubler, *Gaz. hebd.* 1876, p. 332. See also p. 9 of the same journal.

† Ultzmann, *Centralblatt f. d. med. Wiss.* 1877, p. 831.

‡ Städeler, *Annalen d. Chem. u. Pharm.* 1864, Bd. cxxxii. p. 341. According to Städeler, the formula for biliprasin is $C^{32}H^{22}N^2O^{12}$; for bilirubin, $C^{32}H^{18}N^2O^6$. Maly suggests that biliprasin and biliverdin are identical. (*Journ. f. prak. Chem.* 1868, Bd. civ. p. 32.)

§ Schwanda, *Wiener med. Wochenschrift*, 1865, p. 692.

|| Schwanda, *op. cit.* p. 989.

pigment in 100,000 parts of urine. Even if these results be only approximately true, the amount of pigment passed must be very small in comparison with the pigment excreted in health by the liver.

In some cases of jaundice, even when the urine is high coloured and clearly contains abundance of some kind of pigment, no reaction, or no distinctive reaction, with nitric acid can be seen. Prussak believes that this absence of reaction is due to the presence of fever, and that the bile pigments are burnt off or oxydised in the blood so that they can no longer be detected in the urine.* Huppert, again, says that in many cases of jaundice, no pigment but biliprasin can be found during the whole course of the disease, and it is to the absence of any other pigment but biliprasin that the trouble in applying the nitric acid test is due.† These two statements are not contrary, as biliprasin is but a more highly oxydised body than bilirubin; yet Städeler affirms that biliprasin gives all the reactions of bile pigments with nitric acid, saving only that the blue colour is indistinct.‡ Frerichs likewise attributes the failure of the nitric acid reaction to an oxydation either in or out of the body.§ Nitric acid only gives in this case a red colour.

* Prussak, *Centralblatt f. d. med. Wiss.* 1867, p. 97.

† Huppert, *Arch. d. Heilkunde*, 1867, Jahrg. viii. pp. 351 and 476. This writer finds the best plan of recognising even traces of bile pigment in the urine is to precipitate with milk of lime, let the mixture stand, and filter. Some of the precipitate, the size of half a hazel nut, is put into a test tube, and the test tube half filled with absolute alcohol, and dilute sulphuric acid added till the fluid have a distinct acid reaction. A precipitate is slowly thrown down of a greenish colour; and if the fluid be gently warmed, the alcohol itself becomes of a greenish colour. Hilger recommends that 50 to 100 C.C. of the urine be gently warmed, and hydrate of baryta added until an alkaline reaction appear. The precipitate is collected and washed: if sprinkled with nitric acid the well-known colours are seen. Or the precipitate may be heated with solution of carbonate of soda, when the pigments pass into the solution, and it acquires a green or brownish-green colour. (Hilger, *Journal of Chemical Society*, 1876, Vol. i. p. 445.)

‡ Städeler, *loc. cit.*

§ Frerichs, *op. cit.* Bd. i. p. 106.

Lewin states that, when jaundiced urine gives no reaction with nitric acid, the reaction may sometimes be seen on cooling the urine with ice, thus causing a precipitation of the urates, collecting the urates on a filter, dissolving them in warm water, and testing this solution with nitric acid. A beautiful Gmelin's reaction may thus be seen.* These observations closely agree with those of Ernst Bischoff, who found a large amount of pigment thrown down with the uric acid after acidulation.

Although the presence of one element of the bile, the pigment, is plain almost to the unaided senses without chemical help, yet it is quite otherwise with another important element of the bile, the conjugate acids. Before the days of Pettenkofer† and Strecker‡ it was well nigh hopeless to search for these crystalline elements of the bile in the urine. Nevertheless some observers thought they had detected them both in the blood and urine of jaundice. After Pettenkofer, none succeeded§ in finding the bile acids in the urine, notwithstanding many attempts by observers in every way worthy of credit. It was therefore assumed that the bile acids were absent from the urine in jaundice, and it became a matter of importance to explain their absence. Frerichs and Städeler found that after the injection of colourless bile into the veins of animals, the urine was tinged of a high colour, and gave a well-marked reaction with Gmelin's test, showing the presence of bile pigment|| and yet no bile acids could be found in this

* Lewin, *Centralblatt f. d. med. Wiss.* 1875, p. 81.

† Pettenkofer, *Annalen d. Chemie u. Pharm.* 1844, Bd. lii. p. 90.

‡ Adolph Strecker, *ibid.* 1848, Bd. lxxv. p. 1.

§ C. G. Lehmann, however, says (*Lehrb. d. phys. Chemie*, Leipzig, 1853, 2te Aufl. Bd. i. p. 122.) that he has found substances, which give Pettenkofer's reaction, in the blood and urine of persons whose livers did not seem immediately concerned in the disease.

|| Frerichs, *op. cit.* Bd. i. p. 404. I have elsewhere (p. 235.) remarked upon the incorrectness of this observation.

urine. The same observers afterwards found that when sulphuric acid was allowed to act upon the bile acids, a coloured substance was seen, which gave with nitric acid the same play of colours as bile pigment.* Here there seemed a clear way out of all difficulties. The bile acids do not appear in the urine, because they are oxydised in the circulation into bile pigment.

But in 1858, two years after the publication of this last discovery, Hoppe detected in jaundiced urine a notable quantity of choloidic acid, an acid derived from the bile acids, but containing no nitrogen, and yet giving Pettenkofer's reaction.† Later on he demonstrated the presence of nitrogenous derivatives from the bile acids,‡ and last of all, the presence of glycocholic and taurocholic acids themselves, together with cholalic acid, in the urine of jaundice.§

This discovery of the bile acids or their derivatives in the urine was soon after confirmed by Kühne,|| and although at first doubted by some,¶ yet these acids have been so repeatedly found by those who have used Hoppe's improved method of searching for them, that their presence in the urine of jaundice is now generally admitted.

It may be doubted if the total amount of bile acids in the urine have ever been properly estimated. It is at all events so small that Pettenkofer's test applied directly to the urine gives no certain result. Hoppe in a case of acute yellow atrophy found about $\cdot 03$ *per cent.* of cholonic acid;** and Ernst Bischoff gives as the result of three estimations, $\cdot 02$, $\cdot 04$, and $\cdot 05$ *per cent.*

* Frerichs and Städelcr, *Arch. f. Anat. Phys. &c.* 1856, p. 55.

† Hoppe, *Arch. f. path. Anat.* 1858, Bd. xiii. p. 101.

‡ Idem, *ibid.* 1862, Bd. xxiv. p. 1.

§ Hoppe-Seyler, *Centralblatt f. d. med. Wiss.* 1863, p. 337.

|| Kühne, *Arch. f. path. Anat.* 1858, Bd. xiv. p. 315.

¶ Neukomm, *Arch. f. Anat. Phys. &c.* 1860, p. 368.

** Hoppe, *Arch. f. path. Anat.* 1862, Bd. xxiv. p. 8.

This latter observer looks upon .3 grm as the *maximum* of bile acids excreted in jaundice by the urine during the 24 hours,* a result which agrees generally with that of Hoppe-Seyler.

If Pettenkofer's test be applied directly to many urines, a reaction follows which may readily be confounded with that seen in a pure solution of bile acids. Sulphuric acid by itself, without the presence of sugar, will often cause a fine red or purple colour, by inexperienced eyes easily to be mistaken for Pettenkofer's reaction. This is most often the case in a high coloured or albuminous urine, and is not uncommon in perfectly natural urine. Nothing therefore but disappointment and utterly untrustworthy results can be looked for from the direct application of Pettenkofer's test to jaundiced urine. It is a method which should never be adopted. The bile acids must be separated out from the jaundiced urine before their presence can be definitely asserted. Neukomm has found that urine to which 1 *per cent.* of bile acid had been added gave with sulphuric acid and sugar a reaction not to be distinguished from that given with sulphuric acid alone by the same urine to which no bile acid has been added. The Pettenkofer's reaction only became unequivocal when the urine contained .5 *per cent.* an amount greatly exceeding that ever seen in the urine of jaundice.†

To detect the bile acids in jaundiced urine a long preparation is needed. In Hoppe's first experiments, the urine was boiled with milk of lime, then filtered, and again boiled with hydrochloric acid. This undoubtedly causes a large destruction of the bile acids, and the method which is now recommended is as follows: Precipitate the bile acids with acetate of lead from the urine, made faintly ammoniacal: wash the

* Ernst Bischoff, *Zeitschrift f. rat. Med.* 1864, Bd. xxi. p. 140.

† Neukomm, *Annalen d. Chemie und Pharmacie*, 1860, Bd. cxvi. p. 34.

precipitate with a little water, boil it with alcohol, and filter hot. The lead salts of the bile acids are soluble in hot alcohol; a few drops of soda solution should next be added, and the whole evaporated to dryness. This should now be boiled with absolute alcohol, filtered and evaporated to a small volume, and then poured into a great excess of æther. In this way the bile acids may often be crystallised out.*

This process is troublesome, and ill fitted for the wants of the practitioner. Modifications of it have been proposed. A rapid way of testing has been set forth by Strassburg. A piece of filtering paper is dipped into the urine to be tested, to which a little cane sugar has been added. The paper is then dried, and on the centre is let fall a drop of concentrated sulphuric acid. Around the drop of acid a beautiful violet colour forms.† In my own hands, however, this test has proved very unsatisfactory. I have noticed a purplish colour, identical with that seen with jaundiced urine, arise with natural urine, or with urine from patients not known to have anything amiss with their livers.

Hilger recommends a modification of Hoppe-Seyler's method. The urine is mixed directly with basic acetate of lead and ammonia; and the precipitate is then dried at a low heat and again and again warmed with absolute alcohol. The alcoholic extract is decomposed with carbonate of soda, evaporated to dryness, and again taken up by warm alcohol. The bile acid salts are then thrown by æther, in the usual way.‡

By some observers the bile acids are now looked

* Hoppe-Seyler, *Handb. d. phys.- u. path.-chem. Analyse*, Berlin, 1865, 2te Aufl. p. 274.

† Strassburg, *Arch. f. d. ges. Phys.* 1871, Bd. iv. p. 461. See also p. 5 of this work.

‡ Hilger, *Journal of the Chemical Society*, 1876, Vol. i. p. 445. Another method for recognising bile is given by Casali in *La Scienza applicata*, 1876, I. fasc. 6. quoted in *Centralblatt f. d. med. Wiss.* 1878, p. 583.

upon as natural constituents of the urine. Naunyn collected large quantities of natural urine and was able to detect an appreciable amount of bile acids by the process of precipitation with lead.* Fudakowski† Höne‡ and Vogel have§ repeated and confirmed these observations, but their value has been doubted by Wolff.||

The presence of the bile acids in natural urine, if granted, is probably due to an absorption of the bile acids from the intestine, a very small quantity passing through the liver into the general circulation.

It has, however, been asserted of late that in long continued jaundice the liver loses the power of secreting the bile acids, and thus none appears in the urine. Golowin found none either in men or animals.¶ Huppert found the amount much decreased towards the end of a case of acute yellow atrophy:** and Dr. Pye-Smith could find no bile acids in 14000. C. C. of the urine of a patient jaundiced a long time, probably from gall-stones.††

Neither dyslysin, nor glycocoll or taurin has ever been found free in the urine.§§ The first is a product of the decomposition of the bile acids; the two last are important constituents of glycocholic and taurocholic acid.

* Naunyn, *Arch. f. Anat. Phys. &c.* 1868 p. 430.

† Fudakowski, *Centralblatt f. d. med. Wiss.* 1869, p. 129.

‡ Höne, *ibid.* 1874, p. 872.

§ Vogel, *Schmidt's Jahrb.* 1872, Bd. clvi. p. 36. Dragendorff was able to get .7 or .8 grm. of bile acid from 100 litres of urine. (*Zeitschrift f. anal. Chem.* 1872, Bd. xi. p. 467.)

|| F. A. Wolff, *Zur Pathologie des Ikterus*, Diss. Inaug. Königsberg, 1869. Abstract in Henle and Meissner's *Bericht f.* 1869, p. 196.

¶ Golowin, *Arch. f. path. Anat.* 1871, Bd. liii, p. 433.

** H. Huppert, *Arch. d. Heilk.* 1864, Bd. v. p. 255.

†† Pye-Smith, *Trans. of Path. Soc. of Lond.* 1873, Vol. xxiv. p. 251. He does not, however, give the method followed.

§§ Frerichs, *op. cit.* Bd. i. p. 102, note. Ernst Bischoff, *Zeitschrift f. rat. Med.* 1864, 3te Reihe, Bd. xxi. p. 146. Kühne, *Arch. f. path. Anat.* 1858, Bd. xiv. p. 322. I attribute no value to the finding of taurin in the urine by Raczievsky, (Leyden, *Beiträge zur Path. des Ikterus*, Berlin, 1866, p. 33), as the microscope only was used and no chemical test.

Krusenstern sought in the urine for cholestearin in four cases of jaundice as well as in other disorders ; but found none.*

The amount of urea excreted in jaundice has of late years been much studied, especially in Paris. For it would seem likely if Meissner's theory of the formation of urea in the liver be true, that the amount of urea in jaundice would be decreased ; and on these grounds : if albuminous substances be split up in the liver into glycogen, bile acids and urea, then, if the formation of glycogen cease in jaundice, the formation of urea should cease likewise. I have shown that within a few hours after the ligature of the bile ducts glycogen ceases to be found in the liver† and this statement has been confirmed by von Wittich.‡ If then in jaundice no glycogen is formed by the liver, it would seem likely that the urea and bile acids would likewise cease to be made. Now Golowin certainly seems to think that in long-continued jaundice, the bile acids no longer appear in the urine ;§ and the fluid found in the dilated gall ducts after death often gives no reaction with Pettenkofer's test. But these are all cases in which the jaundice has been long continued, and it is denied by none that early in jaundice, bile acids may readily be found in the urine and in the biliary passages. So that notwithstanding Golowin's statement it would seem likely that in jaundice, at all events early in the disease, the bile acids continue to be formed. As to the urea, much doubt formerly existed whether the amount were usually low or natural. Becquerel analysed the urine of three jaundiced patients. In the first, a man, he found

* Krusenstern, *Arch. f. path. Anat.* 1875, Bd. lxx. p. 415.

† Wickham Legg, *St. Bartholomew's Hospital Reports*, 1873, Vol. ix. p. 161.

‡ Von Wittich, *Centralblatt f. d. med. Wiss.* 1875, p. 291.

§ Golowin, *Arch. f. path. Anat.* 1871, Bd. liii. p. 433.

17.923 grm. was excreted in the 24. hours; in the second, a man jaundiced after a violent dispute, he found only 4.037 grm. and in a third, a pregnant woman, markedly jaundiced, 7.933 grm.*

A. Vogel found in a case of cancer of the liver with jaundice that the urea varied from 6.75 to 9.5 grm, a very low amount.† Kölliker and Müller found in a woman aged 25 with simple jaundice that the mean of urea during the jaundice was 20 grm., during convalescence 19 grm., and when in health 26 grm.‡ Leyden, on the other hand, has recorded a case in which the urea once rose to 50 grm. in the 24 hours; three times it is noted between 30 and 46 grm. and it never fell below 23 grm.§ There seems to have been in this case some relation between the amount of water excreted and the urea; the highest readings of urea corresponding to the highest readings of water and *vice versa*. Bouchardat has recorded an extraordinary case in which the readings of the urea were enormously high. A man with simple jaundice, following a sudden great joy, passed 3750. C. C. of urine in the twenty-four hours: the specific gravity was 1031. The amount of solid matter passed was 220.87 grm: the urea 133.6 grm. The jaundice next day was less, and the urea only 89.18 grm. On the third day the jaundice was still less and the urea only 46.94 grm.|| The same observer has recorded another instance of uncomplicated jaundice in which the urea ruled high, 57.2 grm. in the 24 hours.¶

* Becquerel, *Séméiotique des Urines*, Paris, 1841, pp. 413, and 393. There is an old analysis of Braconnot in which he says he found more urea and less phosphate of lime than usual. (*Journal de chimie méd.* 1827, t. iii. p. 480.)

† A. Vogel, *Zeitschrift f. rat. Med.* 1854, Bd. iv. (neue Folge) p. 391.

‡ Kölliker and Müller, *Verhandlungen d. phys. med. Gesellschaft in Würzburg*, 1856, Bd. vi. p. 497.

§ Leyden, *Beiträge zur Path. d. Icterus*, Berlin, 1866, p. 205.

|| Bouchardat, *Annuaire de Thérapeutique*, 1846, p. 328.

¶ Idem, *ibid.* 1869, p. 237.

Genevoix has published 7 cases of simple jaundice in which during the height of the jaundice the urea was markedly increased, falling to the natural standard as the jaundice disappeared. In three of these cases the urea was over 60 grm. in the 24 hours; in two, 55 grm. and in the remaining two, 45 grm. When convalescence was established, the amount fell to 23 or 24 grm. There was no rise of temperature.* Reuflet records another case of simple jaundice in which the attack followed violent anger, and on the third day of the disease the amount of urea was 41 grammes in 1800 C.C. of urine. The amount of urea ruled high until the jaundice began to disappear, when it sank to 27 and 26 grammes in the 24 hours. Reuflet founds a theory on this observation, and those of Bouchardat and Brouardel. He thinks that if there be no injury to the liver cells, but an increase of the circulation in the liver, a state which he assumes in simple jaundice, then the amount of urea is much increased; but if the liver cells be injured, or the circulation become slow, then the urea is diminished.†

Brouardel has analysed the urine of three cases of simple jaundice, and found no increase or decrease of urea. His figures vary from 26 grm. to 32·8 grm. daily.‡ Julius Jacobs has estimated the urea in three cases: in one, complete obstruction of the ducts from a mass of cancer was present, and the amount of urea was on an average of 7 days, 56·525 grm. in the 24 hours. In two other cases it was 28·249 grm. and 27·527 grm. on an average.§ Dr. A. W. Foot found

* Genevoix, *Essai sur les variations de l'urée et l'acide urique dans les maladies du foie*, Paris, 1876, p. 63.

† Reuflet, *Contribution à l'étude du rôle du foie dans la production de l'urée*, Thèse de Paris, 1879, pp. 33 and 54.

‡ Brouardel, *Archives de Physiologie*, 1876, p. 416.

§ Julius Jacobs, *Arch. f. path. Anat.* 1877, Bd. lxix. p. 487.

no decrease of the amount in one of his cases.* Nor did Dr. George Harley in a case of jaundice lasting 18 months find any decrease until a fortnight before the death of the patient.†

In three cases of supposed cirrhosis complicated with jaundice, Valmont found the average of the urea to be in one, 18 grammes, in the second, 15 grammes, in the third, 7 grammes. In a fourth case of jaundice supposed to be due to cancer of the liver, the mean was 13 grammes.‡ Vulpian found in a case of cirrhosis with jaundice, that the mean was 26·849 grm.§

In three cases of jaundice with clay-coloured stools, J. C. Lehmann found the amount of urea decreased during the obstruction to the gall ducts, while it became greater as soon as the obstruction was removed. In the third case, the amount of urea was increased.|| Lehmann explains the diminution by supposing an imperfect digestion of the albuminous matters, probably because the parapeptones are not thrown down. What, however, would be the explanation of the cases in which the urea is increased in amount?

I have made observations upon the urea in ten cases of jaundice. The two cases in which the largest amount of urea was passed were likewise those in which the largest amount of water was passed, and in which the jaundice had been longest and most intense. The mean of the urea in these two cases was 28·387 and

* A. W. Foot, *Dublin Journal of Medical Science*, 1876, Vol. lxi. p. 478. The amount excreted was 439·087 grains.

† George Harley, *Jaundice, its pathology and treatment*, London, 1863, p. 74 *et seqq.*

‡ Valmont, *Étude sur les causes des variations de l'urée dans quelques maladies du foie*, Thèse de Paris, 1879. This thesis has been put together with much diligence, and contains a long series of analyses of the urine, chiefly in cases of cirrhosis. The estimations of the urea were made by the hypobromite process.

§ Vulpian, *Clinique méd.* Paris, 1879. p. 272.

|| J. C. Lehmann, *Ugeskr. for Læger*, 1868, 3 R. vi. No. 24-26. Abstract in *Virchow's Jahresb. f.* 1868, Bd. ii. p. 143.

29.574 grm. The lowest amount of urea was met with in a case of somewhat uncertain diagnosis, in which the jaundice had lasted about two months and the stools were of a light brown; the mean of five consecutive observations was 15.975 grm. In two other cases of jaundice from cancer of the pancreas and liver, the mean amount of six observations was 18 grm. In the remaining five cases, the means varied from 19.8 to 27.28 grm.*

Upon a review of these cases it seemed to me that the amount of urea was the greatest in those patients whose general health was the best, or who were allowed the most generous diet. I do not think there is any proof that obstruction of the gall ducts causes a lessened excretion of urea; although the earlier recorded cases may at first seem to encourage such a belief. Some of the estimations of the urea lately undertaken by the French observers, apparently at the suggestion of Charcot, seem to destroy such a notion. It is, however, a hard matter on any theory to explain the great increase of urea which Bouchardat noted in his cases, and it only remains to remark that according to present observations the urea in jaundice may be low, natural, or greatly in excess; and that the laws which govern the amount of the urea in the urine of jaundice are yet quite unknown.

Baumstark found in the urine of jaundice a homologue of ordinary urea, which he looks upon as the diamide of sarcolactic acid, or the urea of sarcolactic acid. This body is also present in normal urine, but in small quantity.†

There are not many observations on the amount of uric acid daily excreted in jaundice. Becquerel found,

* Wickham Legg, *Med. Chir. Trans.* 1876, Vol. lix. p. 149.

† Baumstark, *Berichte d. deutschen chemischen Gesellschaft zu Berlin*, 1873, Bd. vi. p. 1378.

in one of three cases, the uric acid in excess, as much as 1.153 grm. in quantity,* but in the remaining two it was natural. Kühne seems to think that it is always much increased,† and on the other hand, Ernst Bischoff, whose observations lay claim to far greater accuracy than those of Kühne, found the uric acid not increased.‡ He explains Kühne's statement by saying, that when jaundiced urine is acidulated with hydrochloric acid, an amazing quantity of crystals is thrown down. If these crystals be collected on a filter, they dissolve when well washed with water, and the water gives an intense reaction with nitric acid; so that it is highly probable that the crystals are mostly made up of bile pigment. Dr. A. W. Foot has, however, in one case found an increase of the uric acid, the amount being 27.13 grains.§ Dr. George Harley found .511 and .266 grm., and lastly none, in three analyses made one after another in a case of permanent obstruction.|| In these two last cases the uric acid seemed to diminish or increase *pari passu* with the urea. The like was noticed by Genevoix who found that the uric acid was increased in 7 cases of simple jaundice with the urea, and that as the jaundice diminished the urea and uric acid decreased likewise.¶ Julius Jacobs did not find the uric acid diminish or increase with the urea: his lowest reading is .997 grm. while the urea is 56.525 grm., while in the two other cases the uric acid is 1.0038 and 1.466 to 28.249 and 27.527 of urea.** In Valmont's four cases, three of cirrhosis and one of cancer, the uric acid was, if any-

* Becquerel, *Séméiotique des Urines*, Paris, 1841, pp. 393 and 413.

† Kühne, *Arch. f. path. Anat.* 1858, Bd. xiv. p. 320.

‡ Ernst Bischoff, *Zeitschr. f. rat. Med.* 1864, Bd. xxi. p. 151.

§ A. W. Foot, *loc. cit.*

|| George Harley, *loc. cit.* and: "In non-malignant hepatic disease, especially towards its latter stages, the uric acid is found to be remarkably diminished." (*Urine and its derangements*, 1872, London, p. 71.)

¶ Genevoix, *loc. cit.*

** Julius Jacobs, *Arch. f. path. Anat.* 1877, Bd. lxix. p. 487.

thing, below the bounds of health; but in many analyses it rose and fell with the urea.*

Kühne stated, in the midst of his essay on jaundice, that no hippuric acid could be found in the urine of jaundiced men; and that after benzoic acid, or its soda salts, had been given to jaundiced patients, no hippuric acid appeared in the urine, but only unchanged benzoic acid.† It is well known that if benzoic acid be given to men in health, an equivalent quantity of hippuric acid appears in the urine. Several observers have repeated Kühne's experiments, but all with a negative result.‡ The source of error in Kühne's work seems to be that the urine was not examined while quite fresh, and that the hippuric acid was changed again into benzoic. The hippuric acid may in all cases be found in jaundiced urine, if looked for soon after the urine have been voided, and by the method recommended by Schultzen.

Less attention has been paid to the chlorides than to the uric acid. A. Vogel found them in his case greatly decreased. They were only .16 to .3 grm: in the twenty-four hours.§ In 9 cases of jaundice in which I estimated the chlorides, I found a tolerably close relation to the urea, the chlorides being equal to about one half of the urea in 6 out of the 9. In 2 of these 3 cases the chlorides were decreased; they were both cases of cancer of the pancreas; the chlorides were about 6 grm. to 18 and 22 grm. of urea. In the re-

* Valmont, *Étude sur les causes des variations de l'urée, etc.* Thèse de Paris, 1879.

† Kühne, *Arch. f. path. Anat.* 1858, Bd. xiv. p. 319.

‡ Folwarczny, *Zeitschr. d. k.k. Gesellschaft d. Aerzte zu Wien*, 1859, p. 225.

Schultzen, *Arch. f. Anat. Phys. &c.* 1863, p. 204.

Neukomm, *Frerichs' Klinik d. Leberkrankheiten*, Bd. ii. p. 537.

Huppert, *Arch. d. Heilkunde*, 1865, p. 93.

Horace Chase, *Arch. f. Anat. Phys. &c.* 1865, p. 392. In two of Chase's cases, however, (dogs in whom the bile ducts had been tied) he could not find hippuric acid after the benzoate of soda had been given by the mouth.

§ A. Vogel, *loc. cit.*

maining case, of doubtful diagnosis, of which I have spoken before while treating of urea, the chlorides were estimated on five following days. The first day the urea was 18 grm. to 21 grm. of chlorides, the second day it fell to 17 grm. of urea to 14 grm. of chlorides, and maintained this proportion through the rest of the observations.* I think the first day's very high reading may be caused by some error; or perhaps accidental admixture, seeing the abundance of chloride of sodium in the world.

Julius Jacobs in his three cases found an increase in the chlorides in nearly all: 10·717 grm. in the first, 17·818 in the second, and 14·366 in the third.† In Valmont's three cases of cirrhosis with jaundice, the amount of chlorides was always small; sometimes only two grammes in the 24 hours being passed.‡

There are also few observations upon the amount of sulphates excreted in jaundice. Kölliker and Müller found in an artificially jaundiced dog that more sulphuric acid was excreted than in a sound dog; a fact which seems to them to show that the sulphur of the taurocholic acid passes into the urine. In a case of simple jaundice in a woman, aged 25, they found, however, the sulphuric acid, as well as the urea, diminished.§ It seems doubtful, however, if the decrease of the sulphuric acid be not due to the general state of the patient. Julius Vogel gives as evidence of the state of chronic disease, that in a jaundiced man the amount of sulphuric acid excreted in the 24 hours was only 1·4 grm.|| Ernst Bischoff likewise found the amount

* Wickham Legg, *Med. Chir. Trans.* 1876, Vol. lix. p. 149.

† Julius Jacobs, *Arch. f. path. Anat.* 1877, Bd. lxix. p. 487.

‡ Valmont, *Étude sur les causes des variations de l'urée*, Thèse de Paris, 1879.

§ Kölliker and Müller, *Verhandlungen d. phys.-med. Gesellschaft in Würzburg*, 1856, Bd. vi. p. 492.

|| Neubauer and Vogel, *Anleitung zur qual. u. quant. Analyse des Harns*, Wiesbaden, 1863, p. 327.

of the sulphates diminished, clearly he thinks, owing to the decreased diet.* But he also noticed another more interesting fact. It is well known, from Voit's observations, that the sulphuric acid in the urine does not account for all the sulphur, and that a body containing sulphur is present, probably derived from taurin. Now the amount of sulphur, not oxydised, present in the urine of jaundice is much in excess of what is natural; and the amount of excess is exactly equal to the amount of sulphur in the fæces which Bischoff calculates should be passed during health. So that Bischoff is inclined to think that the same amount of taurin, and therefore of taurocholic acid, is secreted by the liver in jaundice as in health.

I have been able to find only a few observations upon the amount of phosphates excreted: von Haxthausen notes that a jaundiced man, 36 years of age, excreted as a mean of 24 observations, 1.93 grm. of phosphoric acid in the 24 hours; the lowest being 1.364 grm.; the highest, 3.508 grm. The excretion of phosphates appears to be less before noon than afternoon, and more in the night than during the day.† Dr. A. W. Foot found as a result of one observation upon a jaundiced woman, that the amount of phosphoric acid excreted was 58.625 grains in the 24 hours.‡ Julius Jacobs in one case found 1.183 grm. in the 24 hours.§

Except in cases of acute yellow atrophy, leucin and tyrosin are not present in the urine of ordinary jaundice. Great caution should be used in asserting that they are present in the urine in any case. The mere finding of a sediment in the urine which shows under the micro-

* Ernst Bischoff, *op. cit.* p. 150.

† Von Haxthausen, Schmidt's *Jahrb.* 1863, Bd. cxx. p. 160. Braconnot (*Journal de Chimie méd.* 1827, t. iii. p. 480.) says he once found the phosphate of lime decreased.

‡ A. W. Foot, *loc. cit.*

§ Julius Jacobs, *Arch. f. path. Anat.* 1877, Bd. lxi. p. 487.

scope crystals like those of leucin and tyrosin is no proof whatever that these bodies exist in the urine.* Chemical tests must be applied to the bodies crystallised out from the urine, otherwise no reliance can be placed upon the statement that they are present.

Budd† Murchison‡ and Pouzol§ have noticed the occasional presence of casts of the renal tubes in jaundiced urine. Nothnagel looks upon their presence as a constant phænomenon in all cases of intense jaundice, whatever the cause may be. He thinks casts in the urine are more often present than itching of the skin; they are usually hyaline and are then not coloured yellow; epithelial casts are the next commonest, and are deeply yellow coloured; very rare are the so-called fibrinous casts. In two-thirds of the cases albumen was not found by the ordinary tests, nor any of its modifications. The cases observed were catarrhal jaundice, jaundice from gall stones, compression of duct by new growth, pyæmia, and "bilious" pneumonia.|| Dr. Finlayson, in some observations upon the presence of casts in urine not containing albumen, says that tube casts are almost invariably found in marked cases of jaundice, and this as a rule occurs without albuminuria,¶ so that this observer agrees with Nothnagel. In the many cases in which I have carefully looked for casts, I have not been able once to find these bodies. Dr. Finlayson appears to attribute the presence of

* A friend of mine, the late Dr. C. E. Squarey, well known for his experience in the analysis of the urine, was able to get abundant evidence with the microscope of the presence of leucin and tyrosin in nearly all cases of jaundice. Pushing his results further, he got the same shaped crystals in all kinds of urine, diseased and healthy, but he was in no case able to produce any evidence of the presence of these bodies in the urine of jaundice, or of any other disease when using chemical tests.

† Budd, *On Diseases of the Liver*, London, 1857, 3rd ed. p. 288.

‡ Murchison, *Clinical Lectures on Diseases of the Liver*, Lond. 1868, p. 287.

§ Pouzol, *Essai sur l'ictère*, Paris, 1872, p. 18.

|| Nothnagel, *Deutsch. Arch. f. klin. Med.* 1874, Bd. xii. p. 326.

¶ Finlayson, *British and Foreign Med. Chir. Rev.* 1876, Vol. lvii. p. 184.

casts in the urine to the irritation caused by the passage of pigment.

Kussmaul noted in a case of jaundice, supposed to arise from gall stones, crystals of bile pigment within epithelial cells found in the urine. The epithelium was supposed to be shed from the bladder.*

* Kussmaul, *Würzburger med. Zeitschrift*, 1863, Bd. iv. p. 63.

CHAPTER XII.

THE COMPLICATIONS OF JAUNDICE.

Wasting. One long-noticed complication of jaundice is the wasting and weakness.* Even in cases of simple jaundice these symptoms are early observed. Still cases are sometimes seen in which there is scarcely any loss of flesh, and in which the patient feels no weakness even when the disease has lasted a long time. The number of persons with jaundice, seen in places of public resort, shows that in some cases it cannot be attended with any grave inconvenience.

The stoppage of the flow of bile into the intestines is followed by different results according to different observers. Some state that no harm ensues, provided that a free escape of the bile outside of the body be allowed. Others assert that bile is necessary to the digestion, especially of fats, and that if the course of the bile be diverted, death from inanition will sooner or later take place. Be the real state of affairs as it may, it is of importance to note that the glycogenetic function of the liver is abolished within a few hours after the bile ducts are obstructed.† This affords a clue to the wasting and debility which accompany jaundice. The value of glycogen in all processes of growth has long been known, and without the presence of glycogen it is probable that nutrition is seriously interfered with.

Temperature. The temperature in jaundice is commonly natural, or even below the standard of health. Obstruction to the passage of the bile into the intestine

* Hippocrates, *de morbis*, Lib. ii. Cap. xxxix. Littré's ed. t. vii. p. 54.

† J. Wickham Legg, *St. Bartholomew's Hospital Reports*, 1873, Vol. ix. p. 161, and v. Wittich, *Centralbl. f. d. med. Wiss.* 1875. p. 291.

seems of itself to cause no rise of temperature in the body. It is otherwise, of course, if, as a cause of the jaundice, there be a febrile disease, such as pyæmia or abscess of the liver.

Röhrig has shown that after the injection of bile acids into an animal, the temperature becomes greatly lowered,* and it is to the circulation of these in the blood that he attributes the low temperature. It seems to me more reasonable to attribute the symptom to the ceasing of chemical changes in the liver itself. The temperature of the liver is very high, higher than that of any gland in the body, the liver itself being the chief source of animal heat; if the various processes which cause this high temperature come to an end there would be at once a sufficient cause for the general temperature of the body being lowered.

It is worthy of note that if a disease commonly attended with a high temperature, such as pneumonia, for example, be complicated by a jaundice, the temperature no longer shows the usual high reading. Sometimes the temperature shows indeed no rise, even when the disease should be, from its kind, of a markedly febrile character.

Towards the end of a chronic jaundice a sudden rise in temperature may be observed, to as high as 105° or 106° F.† This rise in temperature is always of immediate bad augury,‡ and is often attended with nervous symptoms, such as delirium or coma, and too often the death of the patient follows in a few hours.

The same rise of temperature is seen in *icterus gravis* just before death, and it may very likely be only part of that rise of temperature in the agony which De Haen

* A. Röhrig, *Arch. d. Heilkunde*, 1863, Bd. iv. pp. 392, *et seqq.*

† Gee, *St. Bartholomew's Hospital Reports*, 1869, Vol. v. p. 108. Cf. the case of Charles Kingsley given in full under the head of xanthelasma.

‡ Wunderlich, *Das Verhalten der Eigenwärme in Krankheiten*, Leipzig, 1870, 2te Auflage, p. 404.

observed, more than a hundred years ago, in disorders not attended with jaundice.*

Itching. A general itching of the skin is common in jaundice,† according to Frerichs, in about a fifth of the cases,‡ although I feel disposed to rate the proportion much higher. I have of late inquired of all patients who were jaundiced, whether they had suffered from itching during the time that they were yellow, or immediately before; and I find that out of 48 cases, mostly grown-up men and women, that itching, either general or local, had been felt in 33; that is, a proportion of over 68 *per cent.*

The itching is usually worse at night, sometimes being so severe that the patients tear the skin with their nails, and papules, pustules, and even ulcerations, eczema, or nettle-rash, follow. The sensation of itching is usually spread all over the body, not confined to one particular part, though sometimes it seems to attack the trunk only. It is most severe at night.

The itching is often most intense at the outset of the jaundice, and ceases when the disease has lasted a few days. I have seen, however, the itching in some cases persist through the whole course of the disease, and cause the greatest misery to the patient, destroying sleep.

Graves mentions a case in which the itching of the skin preceded the jaundice by 10 days, and disappeared as soon as the jaundice declared itself.§

He speaks also of a case very like this in the disappearance of the itching when the jaundice set in; but the itching had persisted for two months before the

* Anton. de Haen, *Rat. Med. Vindobonæ*, 1759, Pars iv. Caput vi. p. 211.

† Hippocrates had already noticed this symptom. (*De morbis internis*, Cap. xxxvi. Littré's edition, t. vii. p. 256.)

‡ Frerichs, *op. cit.* Bd. i. p. 113.

§ Graves, *Clinical Lectures on the Practice of Medicine*, Dublin, 1864, second edition, edited by Neligan, p. 637.

jaundice came on. It is quite possible that the two cases may be nothing more than coincidences. Graves thinks that they effectually disprove the current opinion that the itching depends upon the presence of bile in the skin. Dr. Austin Flint describes a case, also in an Irishman, where the itching came on about two months before the jaundice, and was accompanied apparently by urticaria.* In one of my own cases, a girl of 14, the itching came on six weeks before the yellowness was observed.

That the itching of jaundice is sometimes attended by nettle-rash was noticed by Joseph Frank.† Graves speaks of cases of jaundice preceded by inflammation of the joints, in which he was able to foretell the appearance of the urticaria. He looks upon this sequence as invariable: inflammation of the joints, jaundice, urticaria.‡ In a case noticed by Horaczek, the urticaria, with dyspeptic symptoms, seems to have slightly preceded the jaundice.§

It is not known to what cause this itching of the skin is due. As already mentioned, it is thought by some to be owing to the presence of the elements of the bile in the blood. Leyden thinks it caused, not by the inert bile pigment, but by the acids; the fluids of the tissues containing a certain amount of these, cause an irritation of the ends of the sensory nerves in the skin, and thus cause the itching felt by the patients.|| If this theory be true, it would be interesting to know if the urine contain, at the beginning of an attack of jaundice, a larger amount of the bile acids than later on in the disease.

* Austin Flint, *Philadelph. Med. Times*, 1878, Vol. viii. p. 507.

† Joseph Frank, *Prax. med. univ. præc.* Lipsiæ, 1843, Pars iii. Vol. ii. Sect. ii. Fascic. i. p. 279. Cf. Bamberger, *Khten. d. chyl. Systems*, Erlang. 1864, 2te Aufl. p. 472.

‡ Graves, *op. cit.* p. 339.

§ Horaczek, *Die gallige Dyscrasie*, Wien, 1843, p. 141.

|| Leyden, *Beiträge zur Pathologie des Icterus*, Berlin, 1866, p. 106.

Henle suggests on the other hand that the itching may be caused by some fatty change in the secretion of the skin or by a more abundant desquamation of the epidermis.*

Budd looks upon itching as one of the aids to a diagnosis between jaundice from suppression and obstruction, as itching is common in the latter, not in the former.† The same idea is supported by Gubler, who makes the like distinction between his *ictère biliphéique* and *ictère hémaphéique*.‡

Dr. Murchison says that boils and carbuncles are seen in some cases of jaundice.§ Frerichs speaks of a case in which the skin was covered with ring-shaped patches like urticaria. They did not however cause any inconvenience, and disappeared eight days after they were first noticed.|| They could not thus have been xanthelasma.

Slow Pulse. It has been known for many years past that jaundice is often accompanied by a slow pulse, if the patient be free from fever. I am not able to say precisely who was the first to speak of this symptom. Galen describes the pulse in jaundice as smaller, harder, firmer, not weak, nor quick.¶ The slow pulse is spoken of shortly by Corp;** John Andrée certainly describes it and a case in which Dr. Hunter found it as low as 37.†† Portal likewise mentions the symptom.‡‡ It is only, however, of late years that an attempt to

* Henle, *Handb. d. rat. Path.* Braunschweig, 1847, Bd. ii. p. 205.

† Budd, *op. cit.* p. 287.

‡ Gubler, in Laborde, *Phys. path. de l'ictère*, Thèse de Paris, 1869, p. 91.

§ Murchison, *Clinical Lectures on Diseases of the Liver*, London, 1868, p. 291.

|| Frerichs, *op. cit.* Bd. i. p. 114.

¶ Galen, *de pulsibus*, Lipsiæ, 1824, Kühn's ed. Vol. viii. p. 491.

** Corp, *An Essay on the Jaundice*, Bath, 1785, p. 14.

†† John Andrée, *Considerations on Bilious Diseases*, Hertford, 1788, p. 39, note.

‡‡ Portal, *Obs. sur la nature et le traitement des maladies du foie*, Paris, 1813, p. 134. It will be thus seen that Pouzol (*Essai sur l'ictère*, Paris, 1872, p. 74.) was quite wrong when he said that Bouillaud (*Traité de Nosographie méd.* Paris, 1846, t. iii. p. 303.) was the first to notice the slow pulse.

explain this phænomenon has been made. Röhrig first, in 1863, found that the injection of the bile acids into the circulation, not of pigment nor of cholestearin, was followed by a slow pulse. He went further and formed an opinion that the slow pulse was due to the action of the bile acids upon the ganglia of the heart, because the pulse became slow even if the *vagi* were cut and because the heart of the frog when immersed in serum and bile acids beat more slowly than when immersed in serum only.* These reasons would not now be accepted by physiologists as conclusive.

Traube in the following year published an explanation upon altogether different grounds. This is based upon the well-known fact that the bile acids rapidly dissolve the red corpuscles of the blood. The bile acids, therefore, when injected into the jugular vein, destroy a large number of the red corpuscles and render that part of the blood unable properly to exchange oxygen. This damaged part of the blood is rapidly sent through the lungs and brought to the left side of the heart, and thence carried into the coronary arteries of the heart. The muscular walls, being thus fed with blood quite unfit for their nourishment, become unable to contract, and a slow pulse follows. This theory accounts for the rapid disappearance of the slow pulse when once the injection has been ended.† Johannes Ranke likewise has expressed his belief in the muscular origin of the slow pulse. He found that when the bile acids were injected into the aorta of frogs, the muscles became hard and rigid, and did not answer to the electrical stimulus. From this he concludes that the striped muscles alone are concerned in the slow pulse of jaundice.‡

* Röhrig, *Arch. f. Heilkunde*, 1863, p. 385. Also in an Inaugural Dissertation, *Ueber den Einfluss der Galle auf die Herzthätigkeit*, Leipzig, 1863.

† Traube, *Berliner klin. Wochenschrift*, 1864, p. 86; also in *Gesammelte Beiträge*, Berlin, 1871, Bd. i. p. 366.

‡ Johannes Ranke, *Arch. f. Anat. u. Phys.* 1864, p. 340; also in *Tetanus*, Leipzig, 1865, p. 395.

I have published quite a different explanation of the slow pulse.* Johannes Ranke's theory must, I think, be rejected. It is quite true that the bile acids do cause the muscles to become hard and not to answer to the electrical stimulus, but this is due rather to a chemical than a physiological action. The bile acids, even in weak solution, coagulate albumen, and if they be injected immediately into the muscles, it is not surprising that these should become hard from the coagulation of the myosin, and lose all physiological properties. If, however, the bile acids be injected under the skin so that they may act on the muscles by a natural process of absorption, no change is seen in their powers of contraction. The curves traced by the myograph remain natural, no matter how large the dose of bile acids. On these grounds it will be impossible to attribute the slow pulse in jaundice to the failure of the muscular walls of the heart alone. Traube's theory, likewise, however ingenious, wants a basis of fact and must be rejected.

Nor is the pulse due to an excitement of the inhibitory function of the *vagus*: for if this be removed by a small dose of atropin, the slow pulse still arises when the bile acids are introduced into the circulation.

There remains, therefore, only one other factor in the movements of the heart, the ganglia; and if it be safe to argue in this case, *per viam exclusionis*, these should be the means by which the slow pulse of jaundice is caused. When the ganglia are separated from the ventricles by a ligature, no change follows in the alternate rest and action of the ventricle when the bile acids are introduced into it.†

The slow pulse is by no means common in jaundice;

* Wickham Legg, *Proceedings of the Royal Society*, 1876, Vol. xxiv. p. 442.

† For a fuller account, see the chapter on the physiological action of the bile, p. 201 of this work.

even in cases where the temperature is natural, the pulse usually preserves the natural number of beats.* When the pulse is lowered, it does not usually fall very much, the beats sinking to 70 or 60, rarely lower. I have indeed seen the pulse of jaundiced patients as low as 50, and once only as low as 40. Frerichs says he has seen it as low as 21 beats.† It is usually quite regular. It disappears, as Traube remarked,‡ if the patient get up and walk about. The observation must therefore be made when the patient is lying down.

Frerichs likewise remarks that the slow pulse disappears if any inflammatory action set in; and on the contrary, if during the progress of a febrile disorder jaundice appear, the pulse at once sinks to the normal, or below it.§ I have not met with any like instance. Vulpian has seen the palpitations of aortic and mitral disease disappear altogether during an attack of simple jaundice.||

The reason that the slow pulse so seldom makes its appearance in jaundice would seem to be due to the small amount of bile acid circulating in the blood. It will be shown later on that it is in no way probable that the liver secretes any large amount of bile acids in cases of obstruction to the gall ducts, and this is borne out by the fact that a slow pulse in jaundice is not very common, for any large amount of bile acids secreted by

* Hensch remarks that he has never seen a slow pulse in the jaundice of children. Even in cases absolutely free from fever, the pulse was always 100-120. He attributes this to the great irritability of the child's nervous system, and especially to his fear of the physician, which may make up for the depressing influence of the bile acids on the pulse. (*Beiträge zur Kinderheilkunde*, Berlin, 1868, p. 342.) Rehn (*Jahrb. f. Kinderheilkunde*, 1870, Bd. iii. p. 197.) noticed this slow pulse in two children, in an epidemic of simple jaundice. Dr. Hilton Fagge says that he has never seen the slow pulse out of simple jaundice. (*Guy's Hospital Reports*, 1875, Vol. xx. third series, p. 157.)

† Frerichs, *op. cit.* Bd. i. p. 116.

‡ Traube, *loc. cit.*

§ Frerichs, *loc. cit.*

|| Vulpian, *Lçons*, (année 1874.) Paris, p. 143. Cours recueilli par A. Paulier.

the liver and again absorbed, would undoubtedly cause a slow pulse in every case of jaundice, as well as severe accidents in other parts of the œconomy.

With the sphygmograph the pulse in jaundice gives a tracing which shows a very oblique up line, which rises but little, but which is a long time in coming down to the abscissa. The polychrotism is very marked.* Kleinpeter thinks there is some increase of the arterial pressure, though there are cases in which the tension is decreased.†

Gangolphe, in an interesting thesis, has pointed out that a mitral regurgitant murmur accompanies many cases of jaundice, especially those which show the phenomena of a slow pulse. In all cases the murmur was first noticed while the pulse was slow; and, as a rule, the murmur disappeared when the pulse became quicker. The murmur is usually very soft, not harsh, heard with the first sound at the apex of the heart. The murmur is only heard in the axilla when it is very loud. In some cases it is attended by a murmur at the base, and a murmur in the larger arteries. The murmur is intermittent, and does not last after the jaundice has disappeared, thus distinguishing itself from organic murmurs.

The murmur is due partly to a slight dilatation of the heart, but chiefly to a paralysis of the papillary muscles, due to the action of the biliary constituents upon the heart. Gangolphe points out that in some cases a fatty degeneration of the walls of the heart has been noticed in acute yellow atrophy, and in acute poisoning by the bile acids. He does not think that anæmia has anything to do with these murmurs.‡

* Marey, quoted by Straus, *des Ictères chroniques*, Paris, 1878, p. 110.

† Kleinpeter and Lorain, quoted by Straus.

‡ Gangolphe, *Du bruit de souffle mitral dans l'ictère*, Thèse de Paris, 1875. For his general conclusions see p. 41.

It is worthy of note that in some of Gangolphe's cases, a murmur was sometimes developed at the base of the heart and along the great vessels, phenomena usually associated with anæmia. In jaundice the red corpuscles are often decreased in number, and the blood is in a watery, poor state: it would be hard to disbelieve that any tendency to a murmur should not thus be aggravated. It is, however, highly probable that the murmurs are caused by the circulation in the blood of the bile acids, as the murmur is found so constantly associated with a slow pulse. Other poisons which have a direct action upon the heart sometimes cause a transient murmur, for my friend and colleague Dr. Lauder Brunton informs me that he has frequently found a mitral murmur develop in dogs when they were placed under the influence of digitalis. Dr. Brunton, like Gangolphe, attributes the murmur to an imperfect action of the papillary muscles.

I have never myself seen a murmur which passed away with the disappearance of the jaundice, though I have not unfrequently seen jaundice develop in persons already the subject of heart disease.

Fabre says that since the publication of Gangolphe's thesis, he has noticed a murmur over the heart in five out of eight cases of jaundice. He attributes the murmur to a myocarditis caused by the toxic action of the bile acids.*

Potain has other views as to the cause of the murmurs heard in jaundice. He thinks that the liver will be found to hold the same connexion with heart disease that the kidney does, and that in diseases of the liver, especially in chronic jaundice, there will be enlargement of the heart, chiefly of the right side; a dilatation, rather than hypertrophy, with tricuspid incompetence, as a result of the disease of the liver; not I must own as we

* Fabre, *Gaz. des Hôp.* 1877, p. 916.

are now accustomed to think, that the disease of the liver, as nutmeg liver, is secondary to the tricuspid regurgitation.*

Changes in Power of Perception. In some cases of jaundice, the senses of taste and sight seem to suffer, and to give wrong intelligence to the patient. Neither of these phænomena is common, but it is characteristic of the love of the marvellous that upon these two symptoms, the non-medical mind should have fastened as essential.

i. *Bitterness of Taste.* It is said that patients with jaundice sometimes complain of a bitter taste; and in ancient times this was thought to be invariable.† I have myself not met with any such perversion of taste in my own cases. It has been thought to be due to the passage of bilious matters into the mouth,‡ apparently through the saliva; and the behaviour of animals, during the injection of bile acids into their veins, might be pointed out in support of this view. The creatures thrust out their tongues, and lick their lips and jaws as if to rid themselves of a disagreeable sensation.§ I should myself look upon the gastric state which accompanies so many cases of simple jaundice as a more probable cause of a bitter or disagreeable taste rather than the circulation of the bile acids in the blood, or their escape through the saliva, although Dr. Fenwick has attempted to prove that they may not uncommonly be found in the saliva of jaundice.|| Heberden says it is far from uncommon to have all solid and liquid food taste bitter; and speaks of one to whom everything tasted bitter, except oysters.¶

* Potain, reported by Straus, *Des Ictères Chroniques*, Paris, 1878, p. 114.

† M. A. Antoninus, *Thoughts*, vi. 57, Long's Transl. London, 1869, Sec. ed. p. 130. "To the jaundiced honey tastes bitter."

‡ Henle, *Handb. d. rat. Path.* Braunschweig, 1847, Bd. ii. p. 206.

§ See p. 192 of this work.

|| Fenwick, *Lancet*, 1877, Vol. ii. p. 303.

¶ Heberden, *Commentaries*, Lond. 1806, 3rd ed. p. 247.

ii. *Yellow Vision*. In some rare cases of jaundice, all, or only white, objects appear yellow to the patient. The first account of this symptom on record is given by Lucretius, a non-medical writer, who says :

“Lurida præterea fiunt quæcomque tuentur
Arquati.”*

words which have passed into a proverb.† Galen likewise speaks of the symptom, saying that all objects are seen yellow by the jaundiced.‡

Although this symptom is by no means common, yet Sydenham, the pride and glory of English medicine, speaks of it as part of the definition of jaundice, that all objects appear yellow.§ Mercurialis, on the other hand, altogether rejects this appearance as unheard of.|| There can be no doubt, however, of its occasional appearance. I have myself, during three years, met with no less than three cases. Still many writers look upon it as a symptom of great rarity. Peter Frank says that in the course of 54 years, he met with this symptom only five times;¶ and Frerichs says he has never seen a case although he has always asked for the symptom.**

Yellow vision is usually seen only in intense jaundice, and then for no great length of time, for the symptom rapidly passes off. I have, however, seen yellow vision last for three days. As a rule, only white objects appear yellow ; but in some severe cases all objects have a yellow shimmer.

* Lucretius, *de rerum natura*, Lib. iv. 331. Some think that Hippocrates speaks of this symptom, (*De locis in homine* Cap. 16) when, as some read, it is said that jaundice is dangerous when it falls upon the eyes. Littré (his edition of Hipp. t. vi. p. 308.) adopts quite a different construing.

† They are quoted by Montaigne in his long essay on natural religion or apology for Raymond of Sebonde, (*Essais*, Livre ii. Chap. xii.) to show how completely we are at the mercy of our senses. See also Sextus Empiricus, *Pyrrhon. Hypot.* Lib. i. Cap. xiv.

‡ Galen, *De symptom. different.* Cap. ii. Kühn's ed. Vol. vii. p. 99.

§ Sydenham, *Processus Integri*, Cap. xxix. ed. Greenhill, p. 582.

|| Mercurialis, *Var. Lect. in Med. Script.* Venetiis, 1598, Lib. vi. Cap. xii. p. 129.

¶ J. P. Frank, *De curand. hom. morb. epitome*, Viennæ, 1821, Lib. vi. Pars iii. p. 307.

** Frerichs, *op. cit.* Bd. i. p. 115.

The cause of the yellow vision is quite unknown. Many, led by Morgagni,* have thought it to be due to the impregnation of the humours of the eye by bilious fluids. Peter Frank, however, objected to this doctrine on three grounds: i. that he had often seen the cornea yellow without disturbance of vision; ii. that the yellow vision is often intermitting; and iii. that a woman, suffering from typhoid, who had never been jaundiced, saw all things yellow for two days.†

He allows that yellow vision may sometimes arise from coloured humours or membranes of the eye, yet he evidently thinks that the whole phænomenon may well be explained on nervous grounds. Joseph Frank, following his father, points out that the disorder is not unfrequently attended by night blindness, and that it is very possibly due to some changes in the optic nerve.‡ Stokes seems likewise to favour the view of nervous origin.§

Elliotson, on the other hand, made a return to the views of Morgagni. He found that one of his patients who was jaundiced, saw yellow with the left eye, and not with the right; in the left, two large red vessels ran over the cornea; in the right, there was no enlargement of the vessels. Elliotson infers that the serum of the blood passing in front of the eye tinges all things yellow. He had soon after this another jaundiced patient who saw yellow, and in whom the conjunctiva around the cornea was greatly inflamed.|| Sir Thomas Watson, likewise, records the case of a patient who saw yellow,

* Morgagni, *De sedibus, etc.* Ep. xxxvii. Art. 8. Cf. Le Cat, *Traité de la couleur de la peau humaine*, Amsterdam, 1765, p. 161. He found in a case of jaundice the aqueous and vitreous of a yellow tint.

† J. P. Frank, *op. cit.* p. 344.

‡ Joseph Frank, *op. cit.* p. 276. Bamberger (*Krankheiten d. chyl. Syst.* in Virchow's *Handbuch*, Erlangen, 1864, 2te Aufl. p. 473.) remarks that all the cases of day and night blindness, which he has seen associated with jaundice, have died.

§ Stokes, *London Med. and Surg. Journal*, 1834, Vol. v. p. 200.

|| Elliotson, *Lond. Med. Gaz.* 1833, Vol. xii. p. 486.

and who had several varicose and singularly tortuous vessels proceeding across the sclerotica towards the cornea, and some of them reached its margin. He endorses Elliotson's view and thinks that the vessels when enlarged by disease, give a passage to the yellow colouring matter, so that all things appear as if viewed through yellow stained glass.* Dr. Murchison records a case of yellow vision, in which the conjunctival vessels were large both during and after the yellowness of sight.†

Rose has supported Peter Frank's theory of a nervous cause for the yellow vision. In one of his cases he found a marked Daltonism, an inability to distinguish red, as well as a seeing of objects yellow. He found the humours of the eye very imperfectly coloured and dismisses these as a cause of the yellow vision.‡ Unfortunately in this case it was impossible to ascertain if the Daltonism existed in health. Santonin seems to cause a like yellow vision and a like Daltonism. The phenomena of the two may be profitably compared together.

During the last three years I have met with three cases of yellow vision in jaundice. Like Heberden's cases they have all been women.§ In one case an old woman aged 66 was examined with the ophthalmoscope. The beginnings of cataract hindered the disc of the left eye from being seen; in the right the disc was somewhat pink. Nothing else unnatural was seen. There were no enlarged vessels. The skin was intensely jaundiced, the stools colourless; the liver stretched two fingers' breadth below the margin of the ribs. Only white

* Thomas Watson, *Lectures on the Principles and Practice of Physic*, Lond. 1857, Vol. ii. p. 605.

† Murchison, *Clinical Lectures on Diseases of the Liver*, London, 1868, p. 295.

‡ Rose, *Arch. f. path. Anat.* 1864, Bd. xxx. p. 442. Dr. Moxon (*Lancet*, 1873, Vol. i. p. 130) examined 7 cases of jaundice in which there was no xanthopsia, and found the humours of the eye perfectly colourless.

§ Heberden, *Commentaries*, London, 1806, Third ed. p. 242.

things were noticed to be yellow. She died shortly afterwards in her own home.

In a short research which was conducted by Dr. Vincent Harris and myself, the power to judge of colours was tested, without beforehand asking the patient if he saw yellow. 15 patients, suffering from jaundice due to various causes, were examined on the following plan: a sheet of paper upon which were painted many of the various shades of the primary colours was presented to the patient, and he was desired to name the colours as they were pointed out. Particular attention was directed to the judging aright of blue, green, and red. In every case, save two, perfectly correct answers were given, even to minute shades of colour. One of these was an old Irishwoman, and we put little trust in what she told us. The second was a man, aged 21, with simple jaundice, who persisted in stating that green was yellow. After this they were all examined with Rose's instrument* to test their Daltonism; but with this, no change was noted. The patients were likewise examined with the ophthalmoscope with a negative result.†

Since the publication of Stilling's sheets for testing eyes, I have used them in every case of jaundice that I have met with, but I have seen no loss of power in detecting at once the various figures and letters.

Hæmorrhagic Diathesis. In some acute forms of jaundice, and in chronic jaundice which has lasted for a long time and draws towards its end, hæmorrhages from the mucous membranes and under the skin are far from uncommon.

I do not know if the short account given by Hippocrates himself of certain persons who became jaundiced

* For an account of this, see Rose's paper in *Arch. f. path. Anat.* 1863, Vol. xxviii. p. 35.

† Wickham Legg and Vincent Harris, *St. Bartholomew's Hospital Reports*, 1876, Vol. xii. p. 167.

during the course of a fever, but who were relieved by an abundant hæmorrhage, may be looked upon as some description of the hæmorrhagic diathesis in jaundice.* Huxham speaks at length of the hæmorrhagic diathesis in jaundice, saying that the hæmorrhages are not uncommon in the more severe kinds of jaundice, and that the blood comes forth from all the openings of the body, and that the bleedings yield to no remedies.† Richard Bright, in his valuable papers on jaundice, notices that, at the end of the disease the patient becomes drowsy, ecchymosis takes place in various parts, and blood escapes from different surfaces. In the more active and febrile forms, he says, this hæmorrhagic tendency may come on very early and be excessive.‡ The appearance of a hæmorrhagic diathesis has likewise been noted by Budd,§ Bamberger,|| Leyden,¶ Murchison,** and others; it has been made the subject of an essay by Monneret†† and Laugier,‡‡ and numerous single cases will be found scattered through the journals.

The hæmorrhagic diathesis is seen very markedly in the jaundice which accompanies acute yellow atrophy of the liver. It will be fully described hereafter. In chronic jaundice the hæmorrhages rarely appear save

* Hippocrates, *Epidem.* liber i. Cap. viii. Littré's ed. t. ii. p. 642. Hæmorrhages in diseases of the liver were certainly noted by Hippocrates (*Prognostic.* Cap. vii. Littré's ed. t. ii. p. 126.)

† Huxham, *Obs. de Aere, etc.* Londin. 1739, p. 142. The very words of Huxham are quoted by Joseph Frank (*Prax. med. univ. præc.* Lips. 1843, Pars iii. Vol. ii. Sect. ii. p. 314, note) as those of Forestus, a writer of the latter half of the seventeenth century. I have tried to verify the reference (*Obs. et cur. med. et chir. op. omnia*, Rothomagi, 1653, Lib. xix.) given by Frank, but have failed.

‡ Bright, *Guy's Hospital Reports*, 1836, Vol. i. p. 614.

§ Budd, *On Diseases of the Liver*, London, 1857, 3rd edit. pp. 228 and 473.

|| Bamberger, *Krankheiten d. chylopoëtischen Systems*, Erlangen, 1864, 2te. Auflage, p. 584.

¶ Leyden, *Beiträge zur Path. d. Icterus*, Berlin, 1866, p. 108.

** Murchison, *Clinical Lectures on Diseases of the Liver*, London, 1868, p. 294.

†† Monneret, *Arch. gén. de Med.* 1854. Vol. i. p. 641.

‡‡ Laugier, *Des hémorrhagies liées au rétrécissement des voies biliaires*, Thèse de Paris, 1870.

towards the end of the patient's life; they are of a very grave, if not fatal, significance. Epistaxis is an extremely common form of hæmorrhage, and the bleeding is often very abundant. Hæmatemesis and hæmorrhage from the bowel are also very common. Hæmaturia is not nearly so common, but it has been seen* and also traumatic hæmorrhages, as from leech bites.† Petechiæ are often seen on the skin, and after death on the serous membranes. The gums and conjunctiva sometimes bleed and show petechiæ.

The amount of blood lost may be so great as to cause death. The bleedings may begin several months before death‡ and continue with intermissions till the patient either die of the bleedings, or of the cause of the jaundice.

Hæmorrhages have likewise been seen in the meninges of the brain and the ventricles.§ Floodings are sometimes seen; and hæmorrhages into the ovary, into the muscles, in fact into every part of the body.

Hæmorrhages in chronic, as well as in acute jaundice are more common into the stomach and intestine than into other parts, if epistaxis be excluded. In chronic jaundice, this may be explained by the disturbance in the circulation of the liver, a theory adopted by Budd. In *icterus gravis* it is not so easy of solution.

The cause of these hæmorrhages in chronic jaundice is obscure. It is not merely the marasmus which accompanies the disorder, as the hæmorrhages are seen in acute jaundice, or the impoverished state of the blood, as Budd supposes,|| but it seems to be the jaundice itself, that is the bile circulating in the blood,

* Laugier, *op. cit.* p. 11. Monneret, *loc. cit.*

† Laugier, *op. cit.* p. 16. Mettenheimer, *Beiträge zu der Lehre von den Greisenkrankheiten*, Leipzig, 1863, p. 120.

‡ Laugier, *op. cit.* p. 19.

§ Reclus, *Gaz. des Hôp.* 1872, p. 260.

|| Budd, *op. cit.* p. 473.

which is the source of the hæmorrhage. Of the elements of the bile, the only one known to possess any power of begetting hæmorrhages is the bile acids, and it is to the action of the bile acids upon the blood corpuscles that Leyden seems inclined to attribute the phænomena.* Were this the case, hæmaturia ought to be a constant accompaniment of the hæmorrhagic diathesis, just as it is always seen after the injection of bile acids into the circulation; a large amount of hæmoglobin being set free in the plasma of the blood and thrown out by the kidneys.

It is most in accordance with the present state of knowledge to believe that hæmorrhages are preceded by a diseased state of the blood vessels, and it is to the state of blood vessels rather than to the state of the blood that hæmorrhages are due. If this be granted, it will be necessary to search for some cause of disease of the blood vessels in chronic jaundice. Leyden has shown that the bile acids cause a parenchymatous degeneration, not only of the glands, but also of the muscles.† If the middle coat of the arteries share in this degeneration, a sufficient cause of hæmorrhages is set up. It will be interesting to watch, as opportunity offers, for evidence of an extensive degeneration of the vessels in cases of hæmorrhage in jaundice, such as very probably exists in all cases of *icterus gravis*.

A curious hæmorrhagic diathesis often attended by jaundice is seen in the umbilical hæmorrhage of the new-born. Out of 220 cases which Grandidier has collected, jaundice was present in 84; in 35, jaundice and ecchymoses were seen together, and this appears to be a most serious complication, for out of the 35 only 3 recovered.‡

* Leyden, *loc. cit.*

† Leyden, *op. cit.* p. 100.

‡ Grandidier, *Die freiwilligen Nabelblutungen der Neugeborenen*, Cassel, 1871, p. 62.

When hæmorrhages set in during the progress of a case of jaundice, the prognosis becomes very grave, but not, as Laugier asserts, altogether fatal. Monneret and other writers have recorded cases of recovery after epistaxis and even petechiæ.* There are also cases on record of recovery, even when a hæmorrhagic diathesis has set in in cases of umbilical hæmorrhage complicated with jaundice. Fränkel† has published the notes of a very interesting case. A man, aged 31, during the course of a simple jaundice was attacked by hæmatemesis and hæmorrhage from the bowel. He recovered quickly from the jaundice after hæmorrhage had ceased; the day after the hæmorrhage had stopped the urea passed in 24 hours, rose from 10 grammes to 42·17. The chlorides during the highest reading of the urea were small in amount, but rose as the urea fell. The rise in the urea after hæmorrhage is known.

Nervous Symptoms. In nearly all cases of *icterus gravis*, and in most cases of chronic jaundice just before death, delirium and coma, and sometimes convulsions, set in.‡ In some cases the appearance of the nervous symptoms is attended by a rise of temperature.

The cause of these phænomena and the various theories which labour to explain them will be best fully discussed under the head of *icterus gravis*. It may here be stated that many authors believe them to be due to a circulation of the bile elements in the blood, a cholæmia, while others attribute them to a uræmia.

* Monneret, *Arch. gén. de Méd.* 1854, Vol. i. p. 641, and *de l'ictère hém. ess.* Paris, 1859, p. 14, from *Journal de Progrès*.

† Fränkel, *Charité-Annalen*, 1876, Bd. iii. Berlin, 1878, p. 292.

‡ Hippocrates has said: κακὸν δὲ ἐπὶ ἰκτέρῳ μώρωσις (*Praen. Coacae* vi. 194. Littré's ed. t. v. p. 626.) but in modern times Bamberger (*Krankheiten d. chyl.-poët. Systems*, Erlangen 1864, 2te Aufl. p. 473.) was, I believe, the first to point out how common the nervous symptoms are at the end of chronic jaundice. My own experience is completely in accordance with that of Bamberger's. Bright (*Guy's Hosp. Reports*, 1836, Vol. i. p. 609.) says that the patient becomes drowsy in the last stage of jaundice, and that (p. 614) when the disease is more acute and febrile, the nervous symptoms come on early.

Schönlein strangely attributes the delirium to the deposit of bile pigment in the membranes of the brain.*

In nearly all cases of jaundice, although there may be no marked brain symptoms, as delirium, &c. yet there seems a change of humour:† the patients become fretful and peevish. They are disposed to sleep and indisposed to any mental exertion.

Xanthelasma. After jaundice has lasted for some months, there appear, now and then, upon the eyelids, small, oval or rounded, symmetrical patches of the colour and appearance of chamois leather, now called, by the greater number of observers, xanthelasma.‡ *Xanthelasma palpebrarum* is seen in other diseases besides jaundice. Dr. Church has shown its hereditary character,§ and Mr. Hutchinson, who has made a great study of this disorder, has pointed out its connexion with the state called by the older physicians the "bilious state;" that is, headache and vomiting; the seat of the bilious state being the stomach, not the liver. Xanthelasma has also been seen in diabetes; but there seems no good grounds for associating xanthelasma with any special morbid state save jaundice.||

Rayer seems to have been the first to describe and figure xanthelasma;¶ the patient does not seem to

* Schönlein, *Klinische Vorträge*, Berlin, 1842, p. 311.

† Hippocrates speaks of the great irritability of temper in the jaundiced. (*De aff. int.* cap. xxxv. Littré's ed. t. vii. p. 252.) I cannot, however, think that he referred to the delirium of jaundice in the passage where he distinguished between the effect of bile and phlegm. Those who become mad from phlegm are quiet, do not cry out and are not agitated; but those who become mad from bile cry out, are mischievous, and always in movement. (*De morbo sacro*, cap. xv. Littré's ed. t. vi. p. 389. Cf. *Democrit. epist.* t. ix. p. 385.) It seems to me that jaundice is not spoken of, but that madness is explained on the old humoral pathology.

‡ This name was first proposed by Mr. Erasmus Wilson (*On diseases of the skin*, Lond. 6th ed. 1867, p. 773.) It is derived from *ξανθός*, yellow, and *ίλασμα*, metal beaten out.

§ W. S. Church, *St. Bartholomew's Hospital Reports*, 1874, Vol. x. p. 65.

|| Hutchinson, *Med. Chir. Trans.* 1871, Vol. liv. p. 171.

* Rayer, *Traité des Maladies de la Peau*, Paris, 1835, 2e. éd. *Atlas*, pl. xxii. fig. 15. The young man spoken of by Portal, (*Maladies du Foie*, Paris, 1813, p. 121.)

have been jaundiced. The disease was afterwards named vitiligoidea by Addison and Gull.* Within the last 10 years the disease has drawn a great deal of attention both in England and in Germany, Dr. Murchison† and Waldeyer‡ being the first to point out the true histological characters of the spots.

Besides the names of xanthelasma and vitiligoidea, this appearance has been likewise called xanthoma by Frank Smith,§ a term adopted by Kaposi.|| Virchow has proposed to call it *Fibroma lipomatodes*,¶ a name which does not seem to have been followed by anyone, and against which Dr. Pye-Smith has with great justice protested.** *Stearrhæa flavescens* and *molluscum cholesterique* are other names which it is to be hoped will (in like manner) be soon forgotten.

Xanthelasma is not caused save by a long continuance of the jaundice. The shortest time in which I have seen it arise is six months after the first onset of the jaundice, and Dr. Pye-Smith in less than four.†† It is, however, rarely seen earlier than twelve months. It does not seem to be needful that the jaundice should be intense, but that it should be continuous; and what, in cases of jaundice, determines the xanthelasma is quite unknown. It is not dependent on the variety of jaundice, as Mr. Hutchinson thought probable,§§ the disease being seen with a small amount of icteric

who suffered from jaundice for three years, and was then attacked by tubercles or a sort of wart on the back and legs probably had xanthelasma.

* Addison and Gull, *Guy's Hospital Reports*, 1851, Series ii. Vol. vii. p. 265.

† Murchison, *Trans. of the Path. Soc. of London*, 1869, Vol. xx. p. 187.

‡ Waldeyer and Jany, *Sitzbb. d. schles. Gesell. f. vaterländ. Cultur*, Juli, 1868, quoted in Virchow's *Jahresb f.* 1869, Bd. ii. p. 548.

§ W. F. Smith, *Journal of Cutaneous Medicine*, London, 1869, Vol. iii. p. 241.

|| Kaposi, *Hautkrankheiten*, Stuttgart, 2te Auflage 1876, Bd. ii. p. 251. in Virchow's *Handb. d. spec. Path. und Ther.* Bd. iii. Abth. ii.

¶ Virchow, *Arch. f. path. Anat.* 1871, Bd. lii. p. 508.

** Pye-Smith, *Guy's Hospital Reports*, 1877. p. 113.

†† Pye-Smith, *op. cit.* p. 127.

§§ Hutchinson, *op. cit.* p. 181.

staining and bilious stools, as well as with the severe *melasicterus*. Nor is xanthelasma associated with any peculiar disease of the liver; any obstruction to the hepatic duct, without the liver being involved in the disease, may give rise to the skin affection, as Dr. Moxon's case shows.* I think it will prove doubtful if the xanthelasma associated with jaundice be more common amongst men than woman. Mr. Hutchinson found that xanthelasma from all causes was twice as common in women as in men.† Few, however, of his cases were jaundiced. In my own experience, I have met with six cases of jaundice associated with xanthelasma. Four of these were men; two women.

As to the age of the patient, it is generally thought that xanthelasma does not attack young persons. I have, however, met with a case of xanthelasma and jaundice in a girl aged 18 years: Kaposi, a doubtful case indeed without jaundice, in a young man, aged 24, who had patches of xanthelasma the size of wheat corns at the root of the penis,‡ and another doubtful case spoken of by Dr. Pye-Smith in a boy aged 18 associated with jaundice.§ The greatest age at which xanthelasma from jaundice seems to have been observed is Dr. Pye-Smith's case in which the xanthelasma appeared at the age of 57.|| It is hard, however, among the poor to be sure of the age at which xanthelasma appears. Often it happens that they are quite ignorant of the existence of the patches until they are pointed out to them; and this no matter what the cause of the disorder.

Xanthelasma was divided by Addison and Gull into

* Moxon, *Transactions of the Pathological Society of Lond.* 1873, Vol. xxiv p. 129.

† Hutchinson, *op. cit.* p. 175.

‡ Kaposi, *op. cit.* p. 256, note.

§ Pye-Smith, *Guy's Hosp. Reports*, 1877, p. 101.

|| Pye-Smith, *Transactions of the Path. Soc. of Lond.* 1873, Vol. xxiv. p. 250.

vitiligoidea plana, and tuberosa. The flat variety is chiefly met with on the eyelids, commonly on the inner half, and arranged with symmetry on each side. It is seen also in the face and cheeks, on the conjunctiva, and the mucous membranes of the mouth and air-tubes. It may be seen also on the prepuce and *glans penis*,* and even under the nails. They vary from a pin's point to a florin in size; Kaposi says he has seen some as large as a thaler.† They are of a pale yellow white colour, like a dead leaf, slightly raised above the surrounding skin or mucous membrane, soft, and irregular, but tending to the form of a circle. They cause no pain or inconvenience, for the patients are often not aware of their presence.

A variety of the plane is the linear form of xanthelasma, best seen in the palm as white lines following accurately the flexures caused by the bending of the hand and fingers. It is also seen in the soles along the flexures of the toes.

The favourite seats of the tuberosa variety of xanthelasma are the ears, neck, and trunk; the back of the elbows, and hands, knuckles of the fingers; in the ham, knees, and on the feet. It is seen small as a millet seed, or of the size of a horse bean, the patches may seem much larger if individual tubercles become confluent. The skin over the tubercles is smooth, sometimes shining, and moves with them. In some cases of tuberosa xanthelasma of the knuckles, the spots have been adherent to the extensor tendon underneath.

The tuberosa form, unlike the plane, shows a disposition to cause annoyance to the patient. In some cases, tools could no longer be handled, walking and sitting only be accomplished with trouble. There is

* Hillairet, *Bulletin de l'Académie de Méd.* 1878, 42me année, p. 1172.

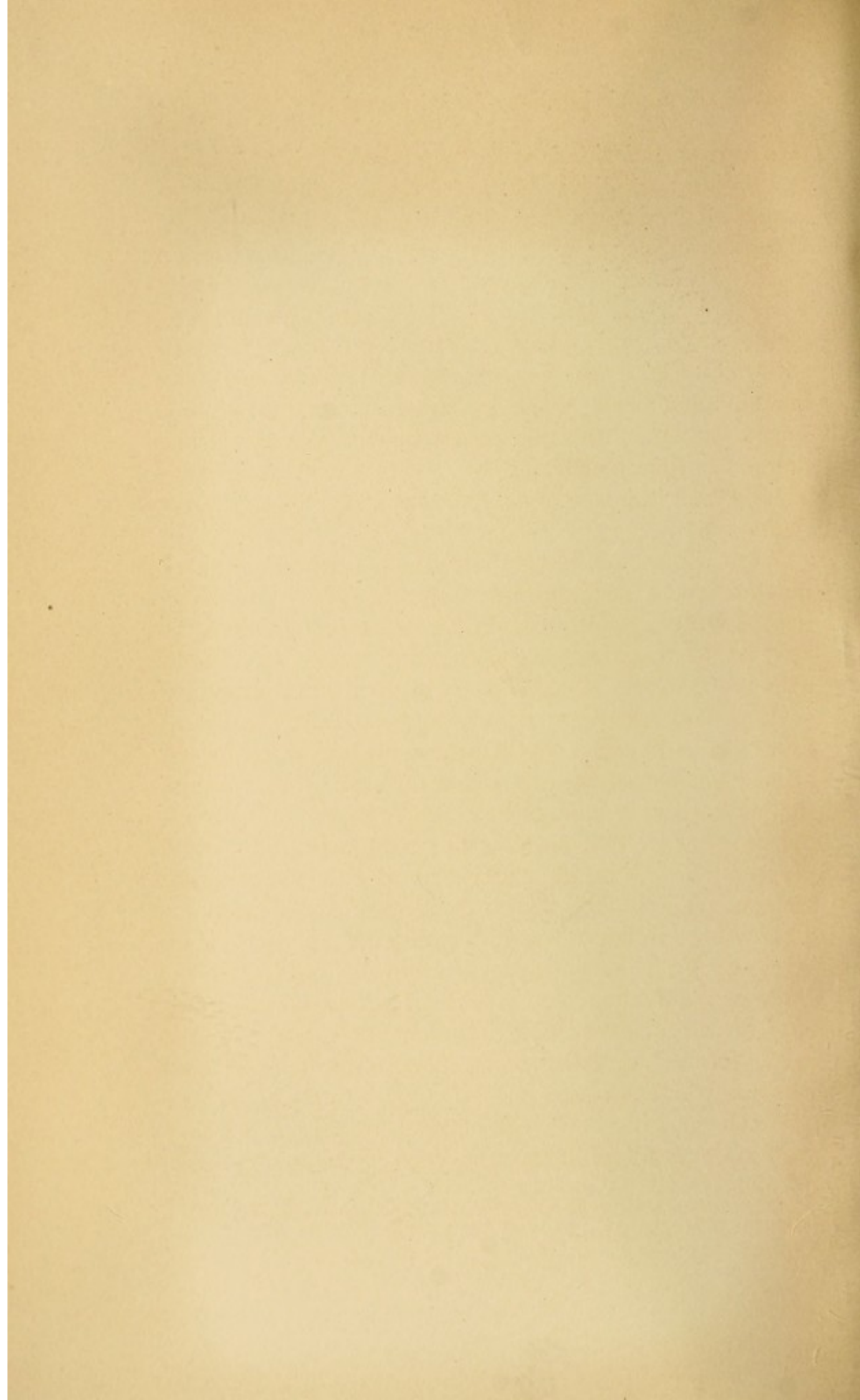
† That is, bigger than our half-crown. Kaposi, *op. cit.* p. 253.



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sometimes a feeling of burning and itching, though it is doubtful how much of this may be due to the presence of the jaundice. The tubercle, if cut across, bleeds profusely.

All forms of xanthelasma show a tendency to symmetry, whether appearing on the limbs or on the mucous membrane. Thus both eyelids are usually affected, both hands and elbows. In a case of my own, the mucous membrane on both sides of the tongue was seized on by xanthelasma in a markedly symmetrical manner. (See No. I. and No. II. of the chromo-lithographs, and the case of Charles Kingsley, at p. 327, of this work.)

Even when jaundice is the cause of xanthelasma, the patches would seem to first appear in the neighbourhood of the eyelids, and in many cases to spread no farther. In much rarer cases the xanthelasma appears all over the body, and is then called xanthelasma multiplex.

As to the nature of xanthelasma: Hebra seems at first to have believed that xanthelasma was due to some sebaceous obstruction, like milium or comedo.* Against this view, it may be urged that when a spot of xanthelasma is cut across, nothing but a bloody fluid can be pressed out, no white accumulation can be removed, and the yellow spot cannot be got rid of by pressure. This view of xanthelasma has, indeed, I think been given up by its author, and the view expressed by Dr. Pavy now prevails. He was the first to examine a nodule of xanthelasma with the microscope, and found it to be formed of a very dense fibrous tissue, pervaded with fat granules.†

Waldeyer was, however, the first to give a full and accurate account of the xanthelasma palpebrarum. He

* Hebra, *Atlas d. Hautkrankheiten*, Lief. 7, and *Diseases of the Skin*, Trans. by Hilton Fagge, *New Sydenham Soc.* 1866, Vol. i. p. 127.

† Pavy, *Guy's Hosp. Reports*, 1866, p. 282.

found that the yellow colour was due in but a very small degree to the increase of the stellate pigment cells which may naturally be found in the eyelids. These cells were met with in numbers only slightly greater than usual. They were found near the epidermis and especially about the hair follicles, vessels, and nerves, yet never so thickly set together that the yellow colour of the xanthelasma patch could be caused by it. The chief change in xanthelasma is a great multiplication of the connective tissue corpuscles in those places where naturally in the eyelid they are more numerous grouped together: therefore around the hair follicles, glands, vessels, and nerves. There follows upon this a fatty degeneration of these new-formed cells. So both these processes together explain the physical characters of xanthelasma, the formation of yellow raised patches. Thus Hebra is quite wrong, as the whole process takes place in the connective tissue of the eyelids, and not in the glands. It is thus an interstitial and not a parenchymatous process. But although xanthelasma has many points in common with dermatitis, new formations in the skin, and syphilis, yet notwithstanding it has something peculiar in itself. The fat, for example, in the new-formed cells is not so granular as in ordinary fatty degeneration, large drops are readily formed; without, however, forming ordinary fat cells. The deposition of fat likewise seems to have no harmful effect upon the cells themselves; as after the fat is taken away by reagents, the cell is always found with nucleus and protoplasm, even after the xanthelasma has lasted many years, and thus Waldeyer has never met with softening, a milky detritus, masses of cholesterolin, or calcification, accidents commonly seen after fatty degeneration. Xanthelasma never seems to undergo a retrogressive metamorphosis, and this is one of its most interesting peculiarities.*

* Waldeyer, *Arch. f. path. Anat.* 1871, Bd. lii. p. 318.

Leber has confirmed these observations in a case of xanthelasma multiplex reported by Virchow. In the smaller tubercles of xanthelasma, however, no fatty infiltration of the cells was to be seen; only a few cells contained a few yellow to yellow-brown pigment granules.* Still it would seem certain that the colour of xanthelasma is due to fat and not to pigment; and this is the more remarkable since jaundice is attended by a deposit of pigment in the skin. Waldeyer's account of xanthelasma palpebrarum may, I think, be safely applied to the xanthelasma of the rest of the body. I have examined patches from the tongue and the scrotum, and found very nearly the same appearances as he has. In the scrotum the cuticle was not thickened over the patches; collections of oil globules in long streaks were seen in the deeper layers of the subcutaneous connective tissue. In some cases there was, as Waldeyer has described, an accumulation of oil globules around the hair follicles, vessels, and other structures passing through the skin; but this was not universally true. The papillæ of the skin seemed unaffected; the collection of oil drops, though somewhat bent towards the papilla as it passed under it, did not enter it. When examined with a high power, the collection of fat drops showed many cells, varying much in size. The very smallest were not so large as a red blood corpuscle, and were round, oval, rhomboidal, and spindle shaped. These small cells were free from granular contents; showing one or even two nuclei. The cells larger than these were slightly granular. Then there were cells four or six times the size of the smallest; round or oval in shape; filled with fat, and therefore no nucleus to be seen. The fat was not in many drops but in one large drop, distending the cell.

Some of these large fat-containing cells had a sinuous

* Leber, reported by Virchow, *ibid.* p. 506.

appearance; apparently brought about by the pressure of the fibres. The patches of the tongue showed appearances in all important respects like those of the scrotum. It is thus evident that the xanthelasma of the mucous membranes and the xanthelasma of the skin are alike in their nature. The same, however, cannot be predicated of the yellow patches seen under serous membranes in cases of multiple xanthelasma. I have examined these spots, which to the naked eye closely resemble those of xanthelasma, and find that the appearance is caused by a spindle-shaped cavity in the connective tissue under the peritonæum, filled with ordinary adipose tissue. These patches, therefore, differ altogether in nature from xanthelasma, and seem to be a mere local accumulation of fat under the peritonæum.

There is, undoubtedly, a superficial resemblance in the process seen in xanthelasma to that of atheroma in the arteries. The great difference between them lies, as Virchow has pointed out, in the absence of any true fatty degeneration.* Both in xanthelasma and atheroma there is a chronic process of cell growth, followed by a fatty infiltration of the cells; but in xanthelasma there is no fatty degeneration; the cells do not, as in atheroma, break up and form a fatty detritus, a change followed in time by the formation of cholestearin, by calcification, and ulceration. Xanthelasma may last for years, and yet the cells, although filled with fat, are perfectly retained, and no retrogressive changes are met with. Mr. Howse, however, has seen, in a case of Dr. Hilton Fagge's, appearances of further degenerative changes, the middle part of the patch, as in atheroma, being converted into lumps of calcareous matter and crystalline bodies.† From these appearances it was

* Virchow, *op. cit.* p. 507. Cf. Waldeyer, *ibid.* p. 322.

† Howse, reported by Hilton Fagge, *Trans. of the Path. Soc. of Lond.* 1873, Vol. xxiv. p. 244.

judged that xanthelasma and atheroma were identical in nature. This opinion can, however, hardly be accepted, as it is opposed to the observation of all other histologists, until many other cases of xanthelasma of the same kind have been examined, and like appearances of fatty degeneration found. The spontaneous disappearance of xanthelasma without scarring is also against the idea of a fatty degeneration.

The greater number of observers, beginning with Dr. Pavy, maintain that there is great over-growth of fibrous tissue in xanthelasma, and on this ground Virchow has proposed to call it *Fibroma lipomatodes* or *molluscum lipomatodes*. In my own case the overgrowth of the connective tissue was not so very apparent: neither does it seem to have greatly struck Waldeyer. A very great development of the fibrous element of the connective tissue would seem incompatible with great cell growth; and xanthelasma, as felt by the finger during life, does not give the impression of hardness. It is probable that one of the distinctions between the flat and tubercular varieties of xanthelasma lies in the amount of connective tissue present.

Another point in which observers differ is the thickening of the cuticle over the patch. Leber* and Dr. Frank Smith† found an increase in thickness of the epidermis; Dr. Murchison found no change in the epidermis,‡ an appearance also met with in a case which I had the opportunity of examining.§ Mr. Howse, indeed, in some specimens of xanthelasma taken from the trachea found no epithelium over the patches, an appearance doubtless due to changes after death, yet some evidence that no increase of epithelium existed during life.||

* Leber, *loc. cit.*

† Frank Smith, *Journal of Cutaneous Medicine*, 1869, Vol. iii. p. 244.

‡ Murchison, *Trans. of the Path. Soc. of Lond.* 1869, Vol. xx. p. 191.

§ See p. 333 of this work.

|| Howse, *loc. cit.*

Within the last twelvemonth Chambard has published a further account of the histology of xanthelasma. His description of the tubercular and plain varieties of xanthelasma differs but little from that given by former histologists; but some details are added as to the state in the tubercular variety of the vessels and nerves, which, he says, have not yet been described. The arteries show an endo-arteriitis, which may block up the bore of the vessel, and the peri-arteriitis, with an active formation of connective tissue, is especially well-marked. The nerve-tubes are soldered together, and the tissue much thickened. Chambard thinks that this implication of the nerves in the xanthelasma tuberosum explains the pain and itching which are felt in this variety, but not in the plane.*

It would seem that the diagnosis of xanthelasma ought always to be easy. The only other skin disease with which it may be confounded is milium or comedo, and from this, xanthelasma may be distinguished by the ready enucleation of the contents of the sebaceous cyst when the skin over it is divided, while nothing can be squeezed out of the patch of xanthelasma but blood and a milky fluid. I do not feel at all confident that some of the appearances figured by Mr. Hutchinson as xanthelasma are not milium. One of the patches has a sebaceous plug in its centre.† It is plain therefore that the diagnosis is not always one which can readily be made.

As to the possible disappearance of xanthelasma multiplex, I have seen a large crop of xanthelasma tuberosum, planum, and lineare completely disappear in three years, and leave no trace or scar behind, so that it could not be thought that the skin had been the seat of such extensive changes, and this without any

* Chambard, *Bulletin de l'Académie de Médecine*, 1878, 42me année, p. 1173.

† Hutchinson, *Med. Chir. Trans.* 1871, Vol. liv. plate iii. fig. 2. Kaposi shares the doubt expressed in the text. (Hebra's *Hautkrankheiten*, 2te Auflage, in Virchow's *Handb. d. spec. Path. u. Ther.* Stuttgart, 1876, p. 252 note.)

change in the jaundice. As the eyelids are the first to suffer, so they appear to be the last to recover, as in this case the man still showed well-marked patches (though much smaller) near the inner angle of the eyelids.* In one of Dr. Hilton Fagge's cases the patient told him that some of the patches had disappeared, apparently in a fortnight;† but on comparing her state with notes taken before, it rather appeared that the disease was aggravated. In Dr. Frank Smith's case the patches certainly grew less.‡

As to the treatment of xanthelasma, no drug is at present known to have any influence in removing the spots. Excision by the knife is certainly to be avoided, especially in the neighbourhood of the eye, where the healing of the wound may lead to eversion of the eyelid.

*Hydatids of the Liver, Omentum, and Recto-vesical Pouch : Jaundice :
Xanthelasma of the Tongue, Eyelids, and Skin.*§

Charles Kingsley, aged 35, a cattle-dealer, married, came to me in September, 1873, at St. Bartholomew's Hospital, as an out-patient. He was then deeply jaundiced, and had been so for nine months. He said he was not a drunkard, and had not had syphilis. He had never felt any pain in his right side. The urine gave a very marked reaction with Gmelin's test. The left lobe of the liver was much enlarged, even down to the umbilicus. The surface smooth, but the edge sharp. There was well-marked xanthelasma palpebrarum, and there were also two yellow spots the size of pin-heads on the palpebral conjunctiva of right eye, and one like these on caruncle of left. There were spots of xanthelasma on palms of the hands and left elbow, on the right ear and left side of the nose. The tongue was purplish; along its sides were patches, yellowish white, oblong, quite soft, but slightly raised: also a yellow spot on the middle line of the roof of the mouth, and another near the lingual vein. (See No. I. of the chromo-lithographs.)

* See p. 337 of this work for the case at length.

† Hilton Fagge, *Trans. of Path. Soc. of Lond.* 1868, Vol. xix. p. 438.

‡ W. Frank Smith, *ibid.* 1877, Vol. xxviii. p. 236.

§ This case has been published in the *Trans. of the Path. Society of London*, 1874, Vol. xxv. p. 155, and in *St. Bartholomew's Hospital Reports*, 1874, Vol. x. p. 244.

This patient was admitted into Matthew's Ward on November 18, 1873.

Dr. Herbert Taylor, who was then house-physician, has furnished me with the following clinical notes.

On admission, the patient said he was quite well up to last October twelve months. He was never jaundiced before that time. He then began to feel weak and depressed, and about the same time he was told he was becoming yellow. During these twelve months he had had remissions of the jaundice, remaining clear-coloured for three or four days together. Such remissions have occurred about twice in a month. He has not suffered any pains whatever till the last six weeks; then, about ten minutes after taking any meal, he is seized with pain as though his bowels were being tied in a knot, at the same time his belly swells, and he suffers from wind. The pain lasts from half an hour to three-quarters. For the last six weeks he has had difficulty in passing his stools, and with this, occasionally a little blood with straining. The stools are always clay-coloured and hard, even in the remissions of the jaundice. Micturition during the last week has been very painful; a small stream, occasionally stopping. Before this the urine was abundant, always dark, and staining the linen, even in the remissions of jaundice.

He has lost flesh considerably during the last year; he thinks about two stone. He has not been a spirit-drinker, but has taken much beer.

His legs began to swell about five weeks ago; they are now much less swollen. His skin does not itch much, chiefly the head itches.

Has always been a healthy man, although exposed to all weathers.

He is married, and has six children. He has never had gonorrhœa.

November 19. A thin, care-worn man, blue eyes, sandy-red hair; lying most comfortably on his back. The whole body coloured of an uniform dark yellow tint. Conjunctivæ yellow, pupils contracted. He does not see nor has he ever seen yellow. On certain parts of his body are patches, irregular in shape, assuming more the form of the parallelogram than the circle, of a pale yellow-white colour, paler than the surrounding integument, denser to the touch, but moving freely with the skin over the subjacent textures; smooth surface, not raised; in size from 1 line by 2 lines to half an inch by half an inch. The parts thus affected are: the inner canthus of each eye and adjacent skin, one in palpebral con-

junctiva of left lower eyelid, one larger over right temporal region (zygoma), on the helix of the right ear, on the nape of the neck; many small patches on ball of thumbs, one on ball of left little finger, ulnar extremity, around the root of the penis at junction of skin of scrotum with abdomen, and in the perinæum; none below this point; in the flexures of the fingers of both hands, but not in the toes; stains of old purpura on lower arms and the legs. Scattered over the abdomen and back, scantily, are pustules, broken down by scratching. In the mucous membrane of the lower lips are two small patches, similar in appearance to the patches seen on the skin. Along each side of the tongue, reaching from behind forwards to the tip, not appearing on the upper surface, are masses of tissue of similar appearance, somewhat symmetrical.

Pulse 72, regular; radial artery atheromatous; temperature 97.8° F. Chest well formed, movements equal on both sides. Heart's apex beats in the third left intercostal space, half an inch above and to inner side of left nipple. Sounds normal. Resonance good from above downwards to lower border of third rib or third interspace on right side; from that level down to two fingers' breadth below margin of cartilages is dulness. On the left side resonance downwards to level of heart's apex; from thence dulness downwards beyond the cartilages to a level of one and a half inches above umbilicus. Posteriorly the liver dulness encroaches on the chest; good breathing sounds over area of resonance.

Abdomen: distended, resonant below the limits of dulness just described down to the pubes and to each iliac fossa, except in left iliac fossa, where is an area of semi-dulness, oval in outline, corresponding to an area of resistance to the touch, which is not so in right iliac fossa. Splenic dulness nil. The dulness in the epigastrium and hypochondria above described corresponds to a tumour which is felt in that situation, the margin of which reaches from the lower border of the ninth costal cartilage on the right side, passes horizontally inwards to middle line, and then passes vertically downwards to an inch and a half above umbilicus, and again extends horizontally to cartilages on left side, where it is lost. Surface smooth and firm. The edge on the right side is thick, on the left quite sharp and firm. There is also a small umbilical hernia, which he has noticed only for a fortnight.

There is a considerable œdema of the feet and ankles.

November 20. Slept fairly, tongue furred, white, moist; very thirsty, good appetite; no nausea. Pulse 76; temperature 97° F. Urine deeply coloured by bile, sp. gr. 1012, acid, a slight cloud of albumen; griping abdominal pain.

21st. Slept badly; no pain; tongue clean, moist. Bowels open twice. Pulse 76.

22nd. Slept well; bowels acted with pain. Pulse 80; temperature 98°.

24th. Slight pain in belly. Pulse 80; temperature 96·6°.

December 1. He has been sitting up during the week; he feels easier; there was more difficulty yesterday in passing his water. A restless night. Tongue clean, moist, red; œdema of legs and feet has increased. Pulse 80, full and regular.

2nd. Slept well; no pain. Slight tenderness in right hypochondrium; vomited this morning after breakfast; tea makes him sick. Pulse 80.

4th (10·30 A.M.). Slept very badly. This morning there is slight wandering; very severe pain over lower abdomen, right groin, end of penis, and down right thigh. He lies coiled upon his left side. Micturition painful; a small stream, but it does not stop in passing; urine, no albumen, bile-stained. Belly very tender; tongue parched, furred; thirsty, drowsy; bowels open. Pulse 130, respiration 30, temperature 106°. At 2 P.M.—Pulse 135, temperature 105·6°. Lies on his right side; knees drawn up; has passed water since the morning.

10·30 P.M. He is quite unconscious. Temperature 102·4° F.

5th (2·30 P.M.). Quite unconscious. Pulse 144; temperature 105·4°.

He died at six in the evening.

Examination eighteen hours after death. Body of a universal deep yellow, and wasted; shins and feet œdematous. Rigor mortis well marked; the veins in skin covering iliac fossæ, Scarpa's triangle, and front of chest already shown by purple lines. No other signs of decomposition.

Well marked xanthelasmic patches on eyelids, right ear (one of these is covered by a scab of dried blood), scrotum, bend of elbows, flexures of hands, neck, and shoulders. Along the furrows of the hands they are seen as long, narrow lines. Over belly are three or four spots covered with dried blood. No other ecchymoses on skin.

Calvaria is natural; dura mater of a deep yellow; longitudinal sinus empty. Membranes and arteries of brain natural; so also ventricles, central ganglia, and rest of brain.

The inside of body quite warm. A layer of fat under skin. The cartilages are white, the ribs green. No fluid in either pleura. A greenish fluid in pericardium. The heart's apex is on

the level of the lower border of third rib, or upper part of third interspace. All the contents of the chest are pushed upwards.

The heart natural; aortic and mitral valves somewhat atheromatous: lungs natural.

Tongue: there is a yellow raised spot, the size of a mustard-seed, on the dorsum. Along each side there are three or four irregular yellowish-white spots. They are sharply defined, varying in size from split peas to a sixpence. Two of those nearest the tip show a loss of substance, and they are also covered with a crust of dried blood. The under surface of the tongue shows two or three yellowish spots the size of mustard-seeds.

The soft palate, pharynx, and lower parts of the œsophagus are free from yellow spots. Just where the œsophagus begins is a cluster of numerous yellow spots for about an inch. There is a yellow spot the size of a mustard-seed at the forepart of the larynx, where the two vocal chords meet. The ridge of the bifurcation of the trachea shows a yellow spot. The rest of the larynx, trachea, and bronchial tubes, which were carefully examined, show no yellow patches which could be confounded with xanthelasma.

The peritonæum, covering the recti on both sides, is speckled yellow with small patches. They are tolerably numerous, and in clusters. Other parts of the peritonæum do not show this appearance.

The great omentum is adherent to the distended bladder. To the left there is a swelling of the size and shape of a grown-up man's kidney. It is within the omentum, but is adherent also to the sigmoid flexure of the colon. Opened it is found to contain an hydatid cyst, which encloses very many small daughter cysts, varying in size from a mustard-seed to a large marble.

The stomach and small intestines are natural. There are no yellow patches either on their mucous or peritonæal surface. The contents of the small intestines quite colourless. The contents of the large intestine are also white and solid; but in many places they have a coating of clotted blood. The mucous membrane of the large intestine from the cæcum to the sigmoid flexure shows innumerable ecchymoses, very fine, and surrounded with fine injection. The rectum natural. Contents colourless, solid, unstained by blood.

The bladder is dilated; it holds about a pint of urine, almost black. This urine gives a decided cloud on applying heat and nitric acid. There is a well-marked green colour with Gmelin's test. It contains urea; something over *·6 per cent.*

Filling the pelvis between the bladder and the rectum, and mak-

ing the removal of these organs difficult, is a tumour the size of a child's head. It proves to be another hydatid cyst, but contains no daughter cysts.

On dissecting the porta of the liver, the portal vein is found to contain fluid blood. Swollen lymphatic glands surround the bile-ducts. The common bile-duct is quite free from colour; so also the cystic. The gall bladder contains about an ounce of a slightly viscid, colourless fluid. This fluid is rendered cloudy by acetic and nitric acids; it is rendered more viscid by caustic soda. Gmelin's and Pettenkofer's tests repeatedly applied give no trace of colour. Half an inch above the opening of the cystic duct, the canal of the hepatic duct is completely obstructed by a swelling from within the liver. Just before the obstruction becomes complete, the duct contains a semi solid mass of green pigment. The duct then passes over the wall of the tumour, and cannot be traced for about an inch. Dissecting beyond the tumour, the hepatic duct, dilated to the size of a man's middle finger, and containing a colourless fluid, is open. It receives many large openings of dilated bile-ducts, which also contain a colourless fluid. Following by dissection these ducts, it is found that those in the left lobe are more dilated than in the right. From those ducts in which the surface has been scraped immediately after their being opened, the scrapings under the microscope show abundance of well-formed cylindrical epithelium. No cylindrical epithelium can be seen in the scrapings from those ducts which have been washed with water or touched with a sponge.

Although the large ducts contain a colourless fluid, and are quite white, yet this is not the case with the smaller. They are stained a pale yellow, and on pressing the liver a yellow fluid can be made to come out of them. No yellow spots can be noticed in any of those opened.

Lying in the body, the left lobe of the liver passes for nearly two inches below the level of the right. Taken out, the liver weighs 140 oz. Its colour is a deep olive green, mottled with yellow; surface smooth. On the upper surface of right lobe, near suspensory ligament, are seen two irregular spots, about the size of penny-pieces, of a yellowish colour; they exactly resemble the spots which may be made by pressure on a natural liver after death. A similar spot exists farther back on the upper surface. A cyst projects at the back of the liver, where it is attached to the diaphragm, in the line of the suspensory ligament. The cut surface of the liver is granular; consistence tough.

There are three hydatid cysts in the liver. The largest, about the size of a cocoa-nut, occupies almost the entire thickness of the right lobe of the liver; presses below on the hepatic ducts and on the upper surface of the liver; it is within half an inch of the peritonæum, and causes the yellow anæmic spots before mentioned. Its contents are colourless; no daughter cysts. Another cyst, the size of an orange, lies immediately behind the first, and contains shrivelled-up membranes and a quantity of dark solid pigment. This cyst communicates directly with the hepatic duct by a short canal, about half an inch long and of the diameter of a fourpenny-piece. The third cyst lies at the back of the liver, and projects to the surface where the liver is attached to the diaphragm in the line of the suspensory ligament. Its contents are colourless; no daughter cysts.

Spleen large; very soft. At one end many yellow spots on capsule.

Kidneys large; cortex broad, swollen; white opaque bundles, perpendicular to the medulla, are seen amidst reddish tissue. The pelvis and ureter of left kidney are much dilated.

Aorta somewhat atheromatous; carotids and iliacs free from any appearance of atheroma or xanthelasma.

The liver-cells were examined with the microscope within an hour of the liver being taken out of the body. Specimens were taken from many parts of the right and left lobes. The cells were all found to present the same characters. Their size and shape were not much altered, but when seen in groups it was difficult to make out their outline. Their contents were chiefly pigment arranged around the nucleus, which was large and contained nucleoli. There were but few fat granules, and no large oil-drops.

Parts of the liver were hardened in spirit and in chromic acid. The increase of the connective tissue in the portal canals was certainly marked, although it was not great. The connective tissue within the lobules was not increased. There were no lymphatic bodies or nuclei present in the connective tissue. It is rare to see so slight an increase in the connective tissue of the liver in cases of long-standing obstruction; the slight increase may be attributed to the nature of the obstruction, the fluid pressure of hydatid cyst.

The patches of xanthelasma were hardened in spirit, embedded, thin sections made with a razor, coloured with carmine or logwood and mounted in glycerine. On examining them with a low power, the cuticle over the patches was seen not to be thickened. In the

deeper layers of the subcutaneous connective tissue were seen lengthened streaks of oil globules. In some specimens there was an accumulation of oil around the air follicles, vessels, and other structures passing through the skin; in others, not. These structures, also, did not seem to share in the disease. The papillæ of the skin seemed affected; that is, the collection of oil drops did not enter the papilla, although it became slightly curved towards it, as it passed underneath.

Examined with a higher power and in preparations teased out with needles, the collections of fat drops were found to contain cells of various sizes. The smallest were not larger than red blood-corpuscles; round, oval, rhomboidal, and inclined to be spindle-shaped. The smallest were free from granular contents and showed only one or two nuclei. Those larger were slightly granular. The largest of all were four or six times the size of the smallest; round, or oval in shape; showing no nucleus and filled by fat, not in many drops but in one large drop, distending the cells. The cells were separated from one another by fibres of the connective tissue, which seemed to be scarcely much increased. Some of the large fat-containing cells had a sinuous appearance, their shape being apparently determined by the fibres.

The yellow patches under the peritonæum differed much from the patches of xanthelasma. The spots were formed by a spindle-shaped cavity in the connective tissue under the peritonæum, holding large ordinary fat cells, supported by an areolar network. The patches under the peritonæum differed essentially from xanthelasma, and were mere local accumulations of fat in the meshes of the connective tissue under the peritonæum.

Jaundice: Xanthelasma Palpebrarum.

Catherine Lynch, 18 years of age, came to St. Bartholomew's Hospital on Oct. 22, 1873, being kindly transferred to my care by my friend and colleague Dr. Lauder Brunton.

She came to the Hospital on account of her jaundice which has lasted over 12 months. She came again on Oct. 30, when she was questioned more at leisure. She then said that she had been ill for $2\frac{1}{2}$ years with feelings of heaviness, sleepiness, and sickliness. She had noticed a swelling in the belly for 2 years and a month. She had menstruated but once; that about fourteen months ago, and the discharge was then very little; she had enjoyed tolerably good health up to the time of falling ill. She had been jaundiced more than fourteen months, but the yellowness had been growing

less for the last six months. The urine brought was not highly jaundiced but gave a distinct green ring with Gmelin's test. Before last week, she said, the motions were yellow; this week they have been very dark.

Examining her more narrowly, she was found to be only slightly jaundiced. There were two symmetrical lines of xanthelasma along the inner half of both lower eyelids; the patches were oval in shape, and their long axis vertical, smooth and soft. She had noticed them for six months. No other patches of xanthelasma were noticed over body or hands. There was a large phlyctenula and much injection of right eye. Also a swelling about the size of a pigeon's egg, elastic, almost fluctuating, in the left parotid region had been noticed for two years. The lymphatic glands below were enlarged. The left tonsil was enlarged; not so the right. The glands in the axilla enlarged; not in the groin. Blood examined with microscope showed no increase of the white corpuscles.

There were many sonorous and sibilant rhonchi all over chest; cough very troublesome; phlegm abundant and yellow. Heart-sounds natural.

The liver was enormously enlarged. Its edge was very hard and could be plainly felt in the right iliac fossa; then the edge began to ascend to the right of umbilicus; about an inch above which is the notch, and the left lobe then passes away along the epigastrium till it be lost under the ribs. Surface of liver generally smooth; but midway between lower border of liver and lower border of ribs is a rounded swelling on surface of liver, smooth and highly elastic. Spleen large and moveable. Belly tender when handled.

Father is a porter at Covent Garden. When a child used to eat abundantly of raw vegetables; but not lately.

She was told to take a draught containing fifteen minims of tincture of squills, and the same of paregoric in an ounce of infusion of cascarilla every four hours, and to stay altogether indoors in a warm room.

She came again on Nov. 3. The cough was much less although she still felt sick after a paroxysm. The jaundice also less and motions reported to be a bright yellow.

On Nov. 6, the elastic tumour in parotid region seemed smaller. It was found to be placed a little behind the ear, more over insertion of sterno-mastoid. There was a swelling also not distinctly circumscribed of whole parotid region, even over the masseter. She had never noticed any change in power of discerning colours: white things, for example, always looked white. Liver unaltered.

On Nov. 10, the cough was altogether gone; but the jaundice was somewhat deeper: the urine also gave a more decided reaction with nitric acid. She was ordered to take a draught containing dilute aqua regia before meals.

On Nov. 17, the jaundice was less marked, and there was less intense reaction with nitric acid on the urine. Still the jaundice was marked although slight.

It was noted on Nov. 27, that the elastic tumour on the liver seemed larger; it was about the size of half a good-sized orange; it was now only a finger's breadth from the lower margin of ribs, and stretched nearer the left edge of right lobe. Pulse 96, standing. The phlyctenula now began to be more troublesome, and in consultation with Mr. Howard Marsh, it was determined to blister her behind the ear. Several spots of erythema nodosum were noticed on arms and one spot on shin; but no more xanthelasma. To take two teaspoonfuls of cod-liver oil three times a day.

On Dec. 4, the eye was better: the liver as before.

On Dec. 11, the eye was again not so well. She was therefore sent to see Mr. Power, the Ophthalmic Surgeon. Since that time, I have not seen her nor have I been able to gather any information about her.

*Jaundice: Xanthelasma Multiplex.**

Mrs. C. aged 36, was an out-patient at S. Bartholomew's Hospital under Dr. Andrew in the spring of 1868.

The patient has been married 17 years. She has had 9 children, the youngest 14 months old, one is dead. She has had 3 miscarriages. Two years ago last December she had a quarrel with her husband and a very great fright; and about a week after, she began to turn yellow. They were then living near Aberdeen, and it would seem that she had had much anxiety and annoyance for some time before. For the last three years she had been subject to flooding. The spots began to appear about six months ago, and were first noticed on the elbows as little spots the colour of the skin. She has had much itching and irritability of the skin, which came on about two months after the jaundice but is not nearly so bad now. At one time she used to be obliged frequently to sponge in cold water, and could not sleep at night. The spots are most abundant on the elbows, palms, and soles; but on the palms, (soles

* This case has been published before in *Trans. of Path. Soc. of London*, 1874, Vol. xxv. p. 259.

not seen) they are very slightly, if at all elevated, resembling rather opaque spots in the skin, which presents a marbled appearance from the very great number. She does not sleep well, but does not know why. The tongue is clean: the appetite uncertain; she used to be fond of fat, but cannot take it now. The bowels are regular, slightly costive. Motions during illness have been light coloured, but for the last three weeks, they have been almost natural. The urine is said to be high coloured. The pulse is 60. She has lost nearly four stone in weight, she used to weigh fourteen stone.

Two or three weeks ago she passed something hard at stool, (? gallstone), and her present improvement seems to date from that. Her complexion is now lighter and the spots are less than they were a few weeks ago.

Jaundice: Xanthelasma Multiplex.

James Piggott, aged 32, came to Saint Bartholomew's Hospital Sept 24, 1873.

He says he is unmarried, but that he has never had syphilis or gonorrhœa. He has been a teetotaler since 1863. He has always enjoyed good health; in 18 years he has only been away from business 2 hours owing to ill-health.

He has been jaundiced now for three months. He has been over anxious of late about business.

Present state. The colour of the skin is a deep sallow unlike ordinary jaundice: the conjunctivæ are blood-shot, and do not at first sight strike observer as being icteric. On close examination they are plainly so. The urine high coloured, but contains no albumen, and on being tested with nitric acid in Gmelin's way, there is no trace of a green colour, nothing but a red ring above the nitric acid is found. The stools are said to be now of a fawn colour; under the club doctor they were dark. Liver dulness (absolute) begins two fingers' breadth below nipple and reaches down to the level of the umbilicus. The liver can be felt below this: it does not cross middle line. It is slightly tender to feel: its surface smooth, save just below the junction of the ribs and cartilages, where a rounded smooth swelling size of a small apple may be felt. The belly somewhat retracted: not tender generally. The pulse is 18 in 15", intermittent about 1 in 18.

There is much itching especially about the thighs at night. He does not complain of any pain. His chief trouble is his weakness and loss of flesh.

To take the nitro-muriatic acid draught.

Oct. 8. Liver dulness as before. Epigastrium slightly tender. The splenic dulness is enlarged and the tip can be distinctly felt under ribs. Pulse 22 in 15", not intermittent but very small. There is no murmur at heart; second sound at base reduplicated. Weight remains about the same.

Oct. 11. The edge of the liver is rounded to feel; motions of a light yellow colour. The conjunctivæ are now markedly jaundiced; the urine bilious, but contains no albumen. A beautiful green reaction is given with Gmelin's test.

Oct. 15. He ate two pears yesterday and has been much purged; does not feel so well in consequence. Jaundice the same. There is no xanthelasma palpebrarum.

Oct. 29. Epigastrium still tender. Liver dulness as before; edge as before; the rounded swelling as before. Jaundice somewhat less. Pulse 18 or 19 in 15". The urine shows no albumen, but a slight green reaction with nitric acid. There is no xanthelasma to be seen anywhere. The man says he feels stronger; tongue very red, cracked across. He goes to-morrow to St. Ives to live.

Dec. 3. He came up to-day from St. Ives, where he has been for the last six weeks. He says he has gained 2 or 3 lb. in weight, but he still complains of itching; the jaundice is now only slightly marked; the urine on the other hand very highly coloured; on boiling and adding nitric acid a faint cloud appears; there is deep green reaction with nitric acid. There is a general bulging of the lower ribs on the right side. The deep liver dulness begins at nipple, but is not absolute for two fingers' breadth below. The dulness now extends below ribs for three fingers' breadth. Tympanitic sound to the left of the middle line. The liver can be felt almost to level of umbilicus. Tip of spleen also distinctly felt. Pulse 20 in 15", not intermittent. Stools now light drab.

Has noticed no changes in perception of colours since illness. The conjunctivæ are much injected. A few yellow spots size of pin's point around inner canthus of eyes.

To continue the draught of nitro-muriatic acid.

Aug. 12, 1876. He came to see me again. For several months past he has been living in North Staffordshire, working at the pottery business. He is in London for the day.

He has now well marked xanthelasma multiplex. There are large symmetrical patches on the inner aspect of both eyelids of the plane variety. On the upper right eyelid is a tuberoso patch size of a pea. There is none on the face or head, if a doubtful spot on the lower lip be excepted. None on front or back of trunk,

until the cleft of the nates be reached; on each side of the upper part of this cleft is an abundant crop of prominent tuberoso xanthelasma. In the middle line of the sacrum there is an oblong patch of xanthelasma planum. On the arms there is none, save about both elbows; the olecranal surface is studded with the tuberoso form; the flexure with the plane. There is one small tuberosity on back of right hand; the flexures of both palms and of the fingers are marked by broadish lines of linear xanthelasma.

There is a patch of plane xanthelasma at base of penis and another in middle line of perinæum. There is none on the thighs and legs. But on the left sole, just where the great toe joins the foot, is a streak of linear xanthelasma.

There is no xanthelasma on tongue; nor as far as can be judged on gums. He wears false teeth.

He has been slightly jaundiced since his last visit. He scratches his thighs much, but says this is due more to habit than real sense of itching. Conjunctivæ still coloured yellow; but the complexion is very peculiar, not jaundiced, but very dark; in a healthy person it would suggest an infusion of black blood. He has black hair. The urine is high coloured and looks bilious. It does not stain white paper yellow, nor does it give a green colour with nitric acid. After being boiled, nitric acid causes an opalescence.

He says he first began to notice the xanthelasma in his hands, the spring of this year; he does not remember in what month. He thought they were due to the cold weather. He has been jaundiced continuously for three years.

The liver dulness now begins two fingers' breadth below nipple and reaches to a finger's breadth above border of chest. In axillary line it reaches to border of chest. It cannot be felt, neither can spleen. The tongue is red and fissured. The appetite is bad. He, however, considers himself stronger and better than he was three years ago.

He was heard from on Jan. 4, 1877: he said: "The white marks upon my hands are less plain, but I have such a habit of rubbing myself and rubbing off any little scar or head which are (*sic*) felt moist when warm."

Oct. 18, 1879. He again reported himself to day. He is still slightly jaundiced and looks thin. He is able to do some light work, such as that of a clerk or book-keeper.

The patches of xanthelasma have everywhere, save on the eyelids, disappeared. The palms of the hands, the elbows, the nates and sacrum, penis and perinæum, and the left toe, are free from all traces of the disease. The skin is quite smooth and supple,

and it is hard to believe that it has been the seat of so extensive a pathological change. Over the elbow there is some roughness, but it is doubtful whether it be more than is common; and there are one or two scars, caused, he says, by his tearing the tubercles out with his nails, which then bled plentifully.

He cannot remember the exact time at which the patches began to go away, but thinks it was about the beginning of 1877. No treatment was adopted with a view to their removal.

There is still the same marked bulging of the lower right ribs, and the liver's thin edge can be felt just under the margin of the ribs; the spleen can also be distinctly felt. The liver dulness begins three fingers' breadth below nipple line, and at the same distance in parasternal line, but very quickly is succeeded by a tympanitic sound.

The urine is still bilious to the eye, but gives no distinct Gmelin's reaction.

CHAPTER XIII.

THE MORBID ANATOMY OF JAUNDICE.

THE body of a person who has died of jaundice very readily decomposes. Even in cold weather, the veins over the belly and thighs may be seen as purple streaks within 24 hours of death. The *rigor mortis* rapidly disappears.

The jaundice of the tissues noticed during life persists after death. Gubler thinks that it is the fibrous tissues only which become stained in jaundice by a sort of elective affinity, like that of madder for young bones.*

Certain tissues remain free from colour even in the most intense jaundice. Such are: the teeth, the hair, the brain, the humours of the eye, the cartilages, an appearance which may specially be noticed in the costal cartilages; not so well marked when the body is first opened, but it may well be seen when the bile pigment in the ribs has been oxydised by the action of the air into biliverdin; the cartilages remaining whitish, while the ribs are deep green. The absence of colour in the teeth and cartilages may be readily explained by the absence of large blood-vessels in their structure. It is not so easy to explain the absence of colour from the nerve-centres and nerves themselves, which are always white.† The fluid in the meninges and in the ventricles of the brain may be deeply yellow, while the substance of the brain itself is free from colour.

* Gubler, in Michel, *De l'ictère hémaphéique*, Thèse de Paris, 1868. p. 8.

† Dr. Murchison (*Lectures on Dis. of the Liver*, London, 1868. p. 285) says that the jaundiced tint penetrates the brain. This is quite contrary to my own experience and to the statements of nearly every other writer that I have consulted. Frerichs indeed says that the brain, when œdematous, may have a yellowish appearance, but this is clearly due to the unnatural presence of serum in the brain, not to the colour of the brain itself.

It is worthy of note that in some cases of secondary malignant tumours in the liver, where the primary tumour, such as cancer of the head of the pancreas, has caused a jaundice, the secondary tumours in the liver are not stained, though in the midst of a highly jaundiced organ. This fact may be compared with the same absence of colour in the fluid of the gall bladder and gall ducts after long-standing obstruction.

In jaundice the first organ to suffer is the liver and its ducts, and to this part of the body the attention of the morbid anatomist must be at first directed. It is of the utmost importance, as Virchow has pointed out,* that the examination of the ducts leading from the liver, the hepatic and common duct, should be made in a particular fashion, otherwise the results gained are of little or no value. The object of the examination is to test the patency of the common duct. This used formerly to be done by opening the duodenum near the orifice of the common duct, and then pressing upon the gall bladder. If the contents of the gall bladder passed into the duodenum, the ducts were judged to be patent during life. This test is exceedingly rough, and cannot be trusted either for negative or positive results. In the first place, if no bile flow out, it does not show that the common duct is obstructed, as the cystic duct may be plugged, and thus no bile from the bladder may pass into the gut; in the second place, if bile flow out, it does not show that there was no obstruction during life, as catarrh, hyperæmia, and œdema, of the mucous membrane of the common duct readily enough disappear after death, while during life a serious obstruction may have existed. Lastly, it does not exclude obstruction of the hepatic duct.

The same objections may be made to the passing of

* Virchow, *Arch. f. path. Anat.* 1865. Bd. xxxii. p. 117. Cf. *Wien. med. Wochenschrift*, 1858 No. 24.

a probe up the duct from the papilla, and seeing if there be any obstruction which cannot be overcome. An improvement on both the foregoing methods is the plan of laying the duct open, and seeing if any gross obstruction, such as a plug of mucus, or tumour pressing on the duct, exist. But in all cases, however, the following will be found a better way: in opening the belly great care must be taken not to disturb or press on the gall bladder or ducts. The large intestine and omentum may be carefully removed, and raising the liver without pressing on the gall bladder, the common and hepatic ducts may now be dissected out. It is most convenient to open the common duct a little above its passage into the duodenum, and with a probe-pointed pair of scissors to follow it first downward into the gut, and then upwards towards the liver. Great attention must be paid to three points in the state of the duct: i. a swollen state of the mucous membrane; it is well known that hyperæmia of mucous membranes readily disappears after death, just as the redness of erysipelas of the skin is lost, and the only *post mortem* signs are the swelling and œdema: ii. a plug of mucus and epithelium at the opening of the duct into the intestine; if this be white and not stained by bile, it is proof that no bile has passed along the duct since the plug was formed: iii. a colourless state of the lower part of the duct near the intestine, while the upper part is stained yellow by bile. This is most important evidence, as it shows that no bile has passed down that part of the duct which is unstained by bile, at all events for several days before.

I have sometimes found that the mere movement of the body after death, such as is necessary in carrying it from one room to another, is enough in some cases of jaundice to send the bile from the gall-bladder down the ducts. Some time ago I was examining a case of

pneumonia complicated by jaundice, and used great care that no pressure should be made on the gall-bladder. Yet on opening the ducts, common and hepatic, they were found deeply stained with a fluid of the same colour and appearance as that in the gall-bladder; no obstruction was found in the ducts or at the papilla. The contents and mucous membrane of the duodenum were stained yellow for about three inches above and below the papilla; but beyond this narrow strip, the contents and wall of the intestine, above and below, were perfectly free from all bile staining. The contents of the small intestine were markedly colourless.

The obstruction to the ducts may also be high up in the liver in the finer ducts, so that they should be carefully dissected, and an obstruction within them may be discovered. Oskar Wyss* and Ebstein† have shown the existence of plugs of mucus in the fine ducts of the liver in cases of poisoning by phosphorus, in which disease the large ducts of the liver are commonly free and coloured. Cornil has shown that even the finest ducts, those just outside the lobules, may be filled by masses of epithelium, and obstruction to the flow of bile caused in this manner.‡

If the obstruction to the bile ducts be permanent and near the duodenum, as, for example, a tumour growing from the head of the pancreas, the ducts outside the liver are commonly found much dilated. The gall-bladder suffers very early and becomes much distended. The ducts themselves may often be seen as large as, or even larger than, the middle finger. In man they do not seem to become tortuous; but it is not uncommon to see this appearance in animals when the ducts have been tied near the duodenum. They

* Oskar Wyss, *Arch. d. Heilkunde*, 1867, p. 469.

† Ebstein, *ibid.* 1867, p. 506, and 1869, p. 379.

‡ Cornil, *Comptes rendus des séances de la Société de Biologie*, 1875, juillet, p. 306.

may attain an enormous size. As an instance of this, there is a case which has become quite classical, because quoted by Morgagni. It is a case by Traffellmann, who found in the body of Daniel, Archbishop of Mainz, that the bile ducts were filled with gall-stones and dilated *instar utriculi*.* Morgagni, in quoting this, has changed the *utriculi* into *ventriculi*,† and every writer up to the present day has quoted this case as one of dilatation of the bile ducts to the size of a stomach. There are, however, well authenticated cases in which the dilatation of the ducts has been quite as great, if not greater, than that imagined by Morgagni. The most extreme case with which I am acquainted is recorded by Dr. Halliday Douglas. In a jaundiced girl, seventeen years of age, a fluctuating tumour could be felt on the right side nearly as low as the ilium. Thirty ounces of fluid were withdrawn by tapping. On examination after death, a sac was found on the right side of the belly, over the front wall of which the duodenum passed as a flat band. The walls of the sac were dense and fibrous, one twelfth to one eighth of an inch in thickness. At the upper part of the sac, the dilated openings of the hepatic and cystic ducts were seen. The hepatic duct within the liver was much dilated.‡

Todd, of Dublin, found in a girl of 14, the hepatic and common ducts so enormously dilated that they contained more than a quart of bile, and formed a sac which reached from the porta of the liver to the os sacrum. The ducts lay behind the duodenum, pancreas, and the root of the mesentery, and covered the

* Traffellmann, quoted by Schenk, *Obs. med.* lib. iii. sect. ii. Lugd. 1644, p. 405. To increase the confusion, the Archbishop is often spoken of as a Prince: it must be remembered that the Archbishops of Mainz were temporal as well as spiritual princes. He was the first of the electoral college of the Roman Empire, and Arch-chancellor of Germany.

† Morgagni, *De sedibus, etc.* Epist. xxxvii. Sect. xlvii.

‡ Halliday Douglas, *Monthly Journal of Medical Science*, Edinburgh, 1852, Vol. xiv. p. 97.

anterior surface of the right kidney and the greater part of the left. The cause of the dilatation was a scirrhus state of the pancreas.*

Frerichs gives a drawing of an immensely dilated common duct, which is in the Museum at Breslau.†

The ducts within the liver suffer latest. They do not dilate to anything like the size of those outside. This is doubtless due to the liver-tissue preventing any very great dilatation.

The ducts may show uniform or saccular dilatations. The former is no doubt the most common. The left hepatic duct has always appeared to me more dilated in proportion to its size than the right. This is probably due to the bulk of the left lobe being less than the right; thus less resistance to the dilating force is offered.

The walls of the ducts themselves are thickened, even to the naked eye. Under the microscope this thickening is seen to be due to a great overgrowth of the fibrous coat. In this, great abundance of lymphatic elements may be found, just as in cirrhosis. Raynaud and Sabourin have lately described as well distinct layers of muscular tissue in the walls of the dilated ducts outside the liver; but the muscular tissue disappeared as soon as the ducts passed into the liver itself.‡ § Frerichs§ and Schäfer|| have been unable to recognise any epithelium on these dilated ducts. Heinrich Mayer,¶ however, speaks of them; and I myself have

* Todd, *Dublin Hospital Reports*, 1817, Vol. i. p. 325. It is worthy of note, as some explanation of the enormous dilatation of the common and hepatic ducts, that in both these cases of Halliday Douglas and of Todd, the cystic duct was obstructed. In Frerichs' case, the gall-bladder was of the usual size.

† Frerichs, *Klinik der Leberkrankheiten*, Braunschweig, 1861, Bd. ii. p. 444. He has used symbols, so it is almost impossible for an Englishman to tell what he means by his measurements.

‡ Maurice Raynaud and Charles Sabourin, *Archives de Physiologie*, 1879, p. 46.

§ Frerichs, *op. cit.* Bd. i. p. 148.

|| Schäfer, *De hydrope ductuum biliarium*, Diss. Inaug. Turic. 1842, p. 9.

¶ Heinrich Mayer, *Mediz. Jahrb. hrsgeg. von d. k.k. Gesellschaft der Aerzte*, Wien, 1872, p. 139.

seen abundance of cylindrical epithelium in cases which I have examined carefully. Charcot and Gombault seem to consider the retention of the epithelium almost a necessary feature in the anatomy of the dilated ducts; the epithelial proliferation, say they, must be very active, and is a sign of the irritated state of the wall of the duct.* I have little doubt that the absence of the epithelium is a *post-mortem* change; the ducts must not be meddled with before the examination; they must not be washed or wiped, or no epithelium will be found.

The follicles which open upon the mucous surface of the gall ducts are usually found dilated and filled with pigment. Raynaud and Sabourin have paid especial attention to the appearance of these follicles in obstruction to the ducts. They find in the connective tissue of the portal canals numerous little bodies, which resemble the section of small racemose glands, and are scattered without order around the bile ducts. They are made up of tortuous tubules lined with a single layer of cubical epithelium, and opening into the larger bile ducts. Raynaud and Sabourin look upon these bodies as either the normal glands of the ducts much hypertrophied, a view which seems to me the more probable; or else that the very small ducts seen naturally in the portal spaces, are prolonged and rolled up into a ball.† They appear to be quite distinct from the developments of the ducts described by Charcot and Gombault, Hanot and others.

The contents of the widened ducts vary much. If the examination be made soon after the obstruction have been set up, the contents will be found to be bile little altered. Later on, the bile becomes thickened and tenacious, and a kind of biliary gravel is thrown down. Should the obstruction continue long, the colouring matters of the bile

* Charcot and Gombault, *Archives de Physiologie*, 1876, pp. 275 and 289.

† Raynaud and Sabourin, *op. cit.* pp. 43 and 48.

are absorbed and leave only a colourless fluid,* at first viscid from the presence of mucus, but afterwards limpid. This colourless fluid has been very little examined. There are but few records of the analysis of the colourless fluid found in the gall-bladder, but there seems to be only one case recorded of any chemical analysis of the fluid from the ducts. In this case Schäfer says it possessed all the physical and chemical properties of the plasma of the blood.† In two cases which I have examined I found no bile acids or bile pigment in the fluid.

The presence of this colourless fluid was formerly looked upon as evidence of the cessation of the secretion of bile, of an acholia, an opinion which even a recent writer has supported.‡ The phænomena are, however, better explained by believing that the fine ducts of the liver have been blocked up by mucus, and thus the bile hindered descending into the larger tubes.

The saccular dilatations of the ducts, and the multiple abscesses of the liver, sometimes caused by obstruction to the ducts, would best be considered under the head of diseases of the ducts themselves.

The state of the texture of the liver itself will next be considered. Soon after the obstruction to the ducts is set up, the liver changes in colour. In some cases of short duration, however, no change in colour is seen. The liver becomes mottled in two shades of yellow, of which the deeper colour is seen in the centre of the lobules, the lighter in the circumference. Under the

* I fear that I am unable to agree with Dr. Hilton Fagge in his statement that 'in jaundice the biliary passages are almost always found to contain, not bile, but, an almost colourless mucus.' (*Guy's Hosp. Reports*, 1875, Vol. xx. Third Series, p. 172). In my own experience the reverse has been the case.

† Schäfer, *loc. cit.* The absence of bile acids from the bile found after death in the gall-bladder would seem to be more common than is generally supposed. Golowin (*Arch. f. path. Anat.* 1871, Bd. liii. p. 420.) says that in two out of 36 cases, no bile acids could be found: both were cases of parenchymatous degeneration of the liver and one was jaundiced.

‡ Moxon, *Trans. of the Pathological Society of London*, 1873, Vol. xxiv. p. 129.

microscope the mottling is seen to be due to an infiltration of the cells of the liver with granules of pigment, the pigment being most abundant in the centre of the acinus around the hepatic vein. I am not acquainted with any explanation of the appearance of bile pigment in the cells of the centre rather than of the circumference. It has seemed to me possible that as the gall-ducts take their rise from the circumference of the lobule, the cells lying nearest to them may be able to discharge their contents more readily than the cells lying in the deeper parts.

In one of his experiments on the bile, Heidenhain allowed a solution of indigo-sulphate of soda to flow under moderate pressure into the bile duct of a living animal. He found the mucous membranes, the conjunctiva, the serous membranes, and the fasciæ to become blue; and even blue urine was passed. But the liver itself was the organ least coloured. By careful observation it could be seen that here and there between the lobules there was a tinge of colour; the lobules themselves being natural. If, at the end of the experiment, the liver were hardened and examined, only the intra-lobular bile ducts and their neighbourhood were found coloured. And if the experiment were broken off, even where the conjunctivæ and urine had become blue, the liver recovered itself and clear bile was secreted. These circumstances make it evident, says Heidenhain, that absorption does not take place within the canals of the lobule in which the bile is secreted, or otherwise the liver would be quite blue; the intra-lobular ducts of Chrzonzczewsky* would be then coloured; but the absorption must take place in the inter-lobular ducts. The place of absorption is therefore different to the place of secretion. The first takes place between the lobules, the second within them. When in jaundice

* Chrzonzczewsky, *Arch. f. path. Anat.* 1866. Bd. xxxv. p. 153.

the liver cells become coloured, it is a secondary not a primary phænomenon, the bile is secreted by the lobules, passed into the intra-lobular ducts and thence into the inter-lobular ducts, through the walls of which it is absorbed, and passes by way of the lymphatics again into the lobules.*

The readiness with which bodies are absorbed from the bile ducts is shown by the following experiment by Picard. He injected a solution of "prussiate of potash" into the stomach of two dogs in full digestion, but the injection was followed by no symptoms of poisoning. The same drug, injected into the bile duct, caused the death of the animal instantly. It is perhaps worthy of note, that no resistance was felt to this injection, but that it passed as readily as into an empty cavity.†

It was noted by Saunders that after ligature of the bile duct the lymphatics coming from the liver were filled with a bilious fluid;‡ and Richard Powell says that in one case of jaundice he saw evident and satisfactory marks of the presence of bile in the thoracic duct.§ More lately an important contribution to the investigation of the manner in which the bile leaves the liver in jaundice has been made by Fleischl. Working in the Laboratory at Leipzig, Ludwig asked him to notice that, in a dog whose bile duct had been tied, the lymphatics from the porta to the *receptaculum chyli* were distended with a yellow lymph which gave Gmelin's reaction. Taking up the matter as a definite research, he found that if the bile duct were tied, and a cannula inserted into the thoracic duct in the neck of a large dog, that the lymph contained abundance of bile acids, but the blood not a trace. Hence it is concluded that the bile, in cases of

* Heidenhain, *Studien. d. phys. Inst. zu Breslau*, Leipzig, 1868, Heft. iv. p. 233.

† P. Picard, *Lyon médical*, 1879, t. xxxi. p. 296.

‡ Saunders, *A Treatise on the Structure, Economy, and Diseases of the Liver*, Lond. 1803, Third ed. p. 112.

§ Powell, *Observations on the Bile and its Diseases*, London, 1800, p. 55.

obstruction of the gall-ducts, passes out of the liver by the lymphatics into the thoracic duct, and thence into the blood. If both the common bile duct and the thoracic duct be tied together, no bile passes into the blood.*

As the obstruction lasts, so the colour of the liver becomes deeper, and finally of a dark green, the central parts of the acinus retaining the deeper tint, even to the end of the disease. With the increased depth in colour, the liver becomes firmer and tougher, and in the last stages of all shows a distinct granular appearance both on section and surface. The liver, which in the early stage of jaundice showed a distinct enlargement, now begins to shrink; and this shrinking, toughness, and granular look, may be due to one and the same cause, an increase in the connective tissue.

The histological changes of the liver in obstruction to the duct had been until lately but little studied,* though at Paris we are told that within the last three years the subject has become the order of the day. This is no doubt owing to the experiments of Charcot on this point, which have everywhere drawn much attention.

Oskar Wyss was the first to pay much attention to this state, and the greater part of his research was devoted to describing the casts of the inter-cellular bile ducts, which may be seen in some cases of jaundice, but are not very common. He describes numerous green or greenish-brown bodies, of a rounded or lengthened shape, sometimes branched, from 2 to 5 micro-milli-

* Fleischl, *Arbeiten aus d. phys. Anstalt zu Leipzig*, 1874. Jahrg. ix. p. 24. He has noticed that many lymphatics leave the liver with the connective tissue of the hepatic vein as well as by the porta.

† The chief writers who have dealt with this point are: Handfield Jones, *Trans. of the Pathological Society of London*, 1854. Vol. v. p. 146. Frerichs, *op. cit.* Bd. i. pp. 122. 139. and 248. Bd. ii. p. 501. Beale, *Archives of Medicine*, 1859. Vol. i. p. 125. Foerster, *Würzb. med. Zeitschrift*, 1861. Bd. ii. p. 161. Klebs, *Handb. d. path. Anat.* Berlin, 1869. Bd. i. p. 425.

meters ($\frac{1}{1000}$ of a millimeter) in diameter, and sometimes reaching 13 micro-millimeters. The bodies are only found between the liver cells, never within them, and sometimes form a complete network between and about the cells.* Oskar Wyss looks upon these bodies as casts of the capillary ducts, varicose from distension with bile, an opinion in which most will be inclined to agree with him. I have myself verified his account of these bodies on several occasions, notably in a case of congenital deficiency of the ducts.†

There are changes, however, which the cells and the capsule of Glisson undergo, and which it will be convenient to describe separately from one another, and also to consider the changes in the capsule of Glisson before the changes in the cells.

There may be found some signs that the older writers suspected changes in the connective tissue of the liver in cases of obstruction to the ducts. Albers, speaking of these cases, describes the parenchyma of the liver as granular, rough, and coloured yellowish-brown; while in one case, he says, the liver was really cirrhotic: it appears that the cellular tissue of the liver is partly atrophied, partly indurated.‡ Andral has recorded a case which, although rendered less valuable by the fact that the patient was a drunkard, yet deserves some attention. The bile ducts were much dilated, and the liver was small, deep green, very dense and granular on the surface and section.§ Yet notwithstanding

* Oskar Wyss, *Arch. f. path. Anat.* 1866. Bd. xxxv. p. 553.

† Wickham Legg, *Trans. of the Pathological Society of London*, 1876. Vol. xxvii. p. 181.

‡ Albers, *Beobachtungen auf dem Gebiete der Pathologie*, Bonn, 1836. p. 19.

§ Andral, *Clinique méd.* Paris, 1839. 4e éd. t. ii. p. 534. Virchow (*Würzb. Verhandl.* 1857. Bd. vii. p. 27.) and Liebermeister (*Beiträge zur path. Anat. u. Klinik d. Leberkrankheiten*, Tübingen, 1864. p. 135.) both seem to have looked upon the irritation caused by gall stones as the cause of the increased connective tissue in the liver. Cf. a case by Dr. Henry Green. (*Trans. of the Path. Soc. of London*, 1872. Vol. xxiii. p. 133.)

these hints as to the granular state of the liver, Oskar Wyss was really the first to assert an over-growth of the connective tissue, and yet he passes it by in a few lines, and says that the increase is never very great, and that no increase of the connective tissue within the lobule has yet been seen.* I agree, notwithstanding, with Oskar Wyss, that in cases of slight and transient jaundice, the connective tissue of the liver in man is not increased. It is, however, far otherwise when the jaundice lasts long and is severe, or if the cause of the jaundice be one which would beget great changes in the portal canals. Thus, the over-growth of the connective tissue is very great in animals whose bile ducts have been tied. The increase is here so great that the liver closely resembles that of a drunkard; the connective tissue is studded with lymphatic corpuscles just as in cirrhosis, and the new connective tissue enters deeply into the lobules.† The same appearances may be met with in man when the obstruction is due to the presence of rough angular gall-stones in the common duct, but especially in those rare cases of congenital deficiency of the ducts. A less overgrowth of the connective tissue may be met with in cases of jaundice from cancer of the head of the pancreas, or tumour pressing upon the liver from the outside. The very least increase of the connective tissue that I have ever met with was in a case of complete obstruction to the

* Oskar Wyss, *op. cit.* p. 559.

† Heinrich Mayer, Stricker's *Mediz. Jahrb. hrsgeg. von d. k.k. Gesellschaft d. Aerzte*, Wien, 1872. p. 133. Wickham Legg, *St. Bartholomew's Hospital Reports*, 1873. Vol. ix. p. 161. Charcot and Gombault, *Archives de Physiologie*, 1876. p. 272. Foà and Salvioli (*Archivi per le Scienze med.* 1877. quoted in *Centralblatt f. d. med. Wiss.* 1878. p. 600.) have repeated this experiment on many animals of different tribes, mammals and birds, but they have not found any noteworthy changes different from those already described.

It is clear that it is only by means of animals that this overgrowth of the connective tissue in jaundice could be demonstrated. Any similar attempt from the liver of man would always be met by the insinuation that the patient was a drunkard.

hepatic duct by a hydatid tumour. In this case the increase of the capsule of Glisson was so slight that there was a complete absence of the lymphatic corpuscles which are nearly always seen in cases of overgrowth of the connective tissue in the liver. This case seems to me to disprove Charcot and Gombault's theory, that the overgrowth is due to the distension of the ducts,* and an early putrefaction of the bile; for here the distension was carried to the utmost, and yet no cirrhosis arose.

The cause of this overgrowth of the capsule of Glisson is obscure. It has been suggested to me that it may be due to the ducts feeling (if such an expression be allowed) the necessity for increased resistance, and thus strengthening themselves by adding fibrous tissue to their walls. This cannot be, however, as in the case just mentioned of hydatid tumour completely obstructing the hepatic duct, there was abundance of dilating force within the ducts, and yet the connective tissue was but little increased in comparison with other cases. I thought at one time† that it was the presence of the ligature in the portal fissure which, in the case of animals, set up a great overgrowth of the connective tissue around the vessels, which extended at last to the liver. In connexion with this view it is interesting to observe that a like overgrowth of the connective tissue is seen when the portal vein has been tied after Oré's method.‡ In fact, an overgrowth of the connective tissue follows many other disturbances of the circulation in the liver, as in nutmeg liver.§ And in the kidney, the same interstitial process is set up

* Charcot and Gombault, *op. cit.* p. 289. Dr. Lionel Beale seems in some degree to favour, by anticipation, Charcot's theory in his case of cirrhosis from obstruction. (*Archives of Medicine*, 1859. Vol. i. p. 127.)

† Wickham Legg, *op. cit.* p. 178.

‡ Solowieff, *Arch. f. path. Anat.* 1875. Bd. lxii. p. 195.

§ Wickham Legg, *Med. Chir. Trans.* 1875. Vol. lviii. p. 345.

where any impediment exists to the flow of urine out of the pelvis. But I have lately met with a case which destroys this theory. In a patient, deeply jaundiced, I found a small cancer, not larger than a hazel nut, placed on the mucous membrane of the duodenum and completely obstructing the flow of bile into the duodenum. Here there was no interference with the connective tissue of the porta; yet the liver was as markedly cirrhotic as I have ever seen it in the cirrhosis from obstruction to the bile.

Charcot and Gombault have found, within the new connective tissue of the livers of animals whose bile ducts had been tied, a developement of the biliary ducts like that described, first by Waldeyer,* and afterwards by Hanot,† in hypertrophous cirrhosis. The account is as follows: Under the microscope is seen a large number of winding tubes, often anastomosing and forming a network with irregular meshes. Their number, size, and general direction, vary according to the point looked at; but three zones could sometimes be distinguished in the portal space, more often only two; a central zone filled by large canals; these are not very abundant, and fill the space in the immediate neighbourhood of the vein; they sometimes are prolonged into the fissure, and then fill the middle part; they are in general separated from the other canals by a broad zone of connective tissue. The central zone is the most often wanting. There is also a middle zone in which smaller canals are found than in the first, often anastomosing, but following, as a rule, a direction perpendicular to those of the vessels which radiate from the lobule; lastly, a third zone, formed by very short canals, starting at a right angle from the foregoing to open upon the lobule in a direction parallel to those

* Waldeyer, *Arch. f. path. Anat.* 1868. Bd. xliii. p. 537.

† Hanot, *Étude sur une forme de cirrhose hypertrophique du foie*, Paris, 1876.

rows of liver cells with which they seem in certain places to be continuous. These canals are the least in size of all. The contents of the canals are variable. Sometimes they are completely filled with small epithelium cells; sometimes they form on the inner surface an irregular lining, with all the intermediate stages between the cubical epithelium of the fine interlobular canals and the cylindrical epithelium of the larger ducts. When the canal possesses a free cavity, it is sometimes very narrow, sometimes dilated. In the first case the epithelium is large, in the second flattened. Lastly, in the larger canals, the cavity may be obstructed by a mass of pigment. § I can attest that these rudimentary biliary ducts are seen in cases of obstruction; for I have recently had the opportunity of verifying Charcot and Gombault's statements in some cases of well-marked cirrhosis from this cause.

It is clear that, if the increase of the connective tissue within the liver be at all great, the size of the lobule must decrease; Charcot and Gombault found this really was the case. In the advanced cases the shape of the lobule was much changed, and in a curious way. The lobule is not merely, so to speak, pushed back by the developement of the new connective tissue; in the most wasted of all the lobules the hepatic cells kept shape and size, and even their regular mode of arrangement. They are still seen in rays around the hepatic vein, but at the circumference of the lobule they are stopped abruptly, and each ray differs in length so that the outline of the lobules becomes very irregular. I fear that I am quite unable to corroborate the statements of Charcot and Gombault in this particular. In my own experiments one of the first and most striking results, was the destruction of the natural appearance of the cells arranged in rays around the vein. The cells were

* Charcot and Gombault, *op. cit.* 1876. p. 278.

piled irregularly one on another without any arrangement, and the atrophy of the individual cell was a marked feature in the later cases.

The changes which take place in the cells have been studied by Oskar Wyss,* Heinrich Mayer,† Leyden,‡ and others. Leyden asserts, basing this statement on the results of the ligature of the bile ducts in more than 20 dogs, that the cells of the liver undergo a fatty infiltration as the chief change. In this he is supported by Hayem and Cornil.§ The cells in the centre of the acinus were quite as much filled with fat as those in the circumference. It is to be noted that the bile contained fat drops, and the epithelium of the gall bladder and kidney both showed a fatty infiltration. Oskar Wyss, Heinrich Mayer and myself did not find any high degree of fatty infiltration present. In my own cases I found a certain amount of fatty infiltration of the outer zone of the lobule, if death took place a short time after the obstruction was set up: but if later, very little fat was present in the cells; and, on the contrary, the two observers mentioned, and myself, found a wasting of the cells. They became much smaller than in health, they had granular contents and an indistinct looking nucleus, which Heinrich Mayer says is altered, without more specially stating the nature of the change. In several of my cases I have been unable to detect a nucleus, but I think this to be due to some optical defect rather than to a real absence of the nucleus. Charcot and Gombault found a fatty infiltration quite the exception.||

They are unable to state how the liver cell is de-

* Oskar Wyss, *loc. cit.*

† Heinrich Mayer, *loc. cit.*

‡ Leyden, *Beiträge zur Pathologie des Icterus*, Berlin, 1866. p. 83.

§ Hayem and Cornil, *Comptes rendus des Séances de la Société de Biologie*, Année 1875. p. 309.

|| Charcot and Gombault, *Archives de Physiologie*, 1876. p. 281.

stroyed. The protoplasm gradually decreases, the cell lessens in size and becomes angular in shape, the contents being homogeneous, shining, and slightly yellow, like glass. The protoplasm does not colour with carmine, but the nucleus does. Charcot and Gombault call this the vitreous degeneration. I have seen this appearance in my experiments, but I do not look upon it as very common.

Chambard has repeated the experiments of Charcot and Gombault upon guinea pigs and has come to results closely allied to theirs.* He has paid special attention to the changes undergone by the cells, and points out the presence of many "transparent spots," as he calls the masses of cells which show the vitreous change described by Charcot and Gombault. Chambard discusses the question if these transparent spots be due to the bursting of a bile duct and the action of the bile upon the cells in the neighbourhood; but rather inclines to the belief that the appearance is caused by the filling of the cells with mucus.

In a few cases of permanent obstruction to the ducts the liver cells have been completely destroyed, just as in acute yellow atrophy, nothing but a granular and fatty detritus being seen under the microscope. This appearance is very rare, and has gained undue prominence from the circumstance that in the very first case in which the liver cells were found dissolved, there was a complete obstruction to the ducts.† To explain this solution of the cells, it was thought by Theodor von Dusch that the bile had the property of dissolving the liver cells,‡ but it has been satisfactorily disproved

* Ernest Chambard, *Archives de Physiologie*, 1877. p. 718. and *Laboratoire d'Histologie du Collège de France, travaux de l'année 1877-78*, Paris, 1879, p. 31.

† Thomas Williams, *Guy's Hospital Reports*, 1843. p. 444.

‡ Th. von Dusch, *Untersuchungen and Experimente als Beiträg zur Pathogenese des Icterus*, Leipzig, 1854. p. 36.

by Kühne* and others,† that the liver cell is not dissolved by the bile acids, but that its outline merely is rendered indistinct and faint, but may be readily restored by adding colouring matter to the slide. Oskar Wyss thinks the liver cells in jaundice are more easily destroyed by *post-mortem* decomposition: he says he has been unable to find liver cells from a case of jaundice 48 hours after death.‡ This cannot be generally true, as I have kept jaundiced livers even in hot weather for 7 days, and yet at the end of that time been able to recognise the cell. Leyden has found that a parenchymatous degeneration of the liver and other glandular and muscular organs follows the poisoning by bile acids.§ It would be well to keep his observations in mind when seeking for an explanation of the dissolution of the cells, as a parenchymatous degeneration may end in a complete disappearance.

Frerichs has very fully described the important changes seen in the kidneys. No one before him seems to have paid any attention to their histology in jaundice. As the greater part of the bile pigment leaves the body by the urine, it is natural to expect corresponding changes in the kidneys. After a long-continued jaundice, Frerichs finds the kidneys of an olive green tint; on the surface are seen a few convoluted tubes of a dark colour while in the pyramids, the tubules are brown or green and filled with black deposit. With the microscope, it is seen that the paler tubules are coloured green or brown. The epithelium, rarely completely retained, is coloured deep brown, especially the nucleus. The cells themselves appear some blood red, some green, some brown. Others show layers of pigment arranged

* Kühne, *Arch. f. path. Anat.* 1858. Vol. xiv. p. 334.

† Robin, *Mémoires lus à la Soc. de Biologie*, année 1857. p. 14. See also my own observations, *S. B. H. Reports*, 1873. Vol. ix. p. 180.

‡ Oskar Wyss, *loc. cit.*

§ Leyden, *op. cit.* p. 60.

in a concentric manner around the nucleus. Epithelium showing marks of fatty degeneration may often be seen of a red, brown, or black colour. When the deposit of pigment has reached its highest degree, the tubules appear filled with a coal black, firm brittle mass. This, like some kinds of black gall stones, resists the action of caustic potash for a long time. Sometimes this deposit of pigment is seen everywhere throughout the kidney, beginning in the *Mapighian* bodies where it is less marked, and passing through the convoluted tubes till it reaches the straight tubules of the pyramid, which are often plugged with coal-black masses of pigment.*

I can endorse these statements of Frerichs; I have seen all that he describes and have very little to add. In some cases there has appeared to me an overgrowth of the connective tissue of the kidney; but this I look upon as an accident, as in a child which had been jaundiced from birth, there was no increase of the connective tissue of the kidney. The striation of the cortex is often perfectly retained in these cases, and the kidney simply looks jaundiced.

Möbius has studied the state of the kidney in jaundice, and endeavours to supplement Frerichs' work on this subject. If a moderate amount of jaundice have lasted a few months, the kidneys will be found of the natural size and consistence, and the surface will be smooth and yellow. No change will be seen in the relation between the pyramids and cortex: this last shows a diffuse yellow colour, which Möbius compares to mustard. The pyramids show dark green stripes, the colour of which is most intense midway between the apex and base. If the jaundice have lasted but a short time the colour is much less marked; while if there have been a complete obstruction to the gall

* Frerichs, *op. cit.* Bd. i. p. 107.

ducts, the cortex is dark yellow ochre, some parts being olive green and the green lines of the pyramids very prominent, becoming in some places black. A scraping of the organ shows under the microscope bright yellow granules of varying size, some free, others in epithelium cells. On hardening the organ, the following appearances can be made out: The glomeruli are entirely free from pigment in all cases: so also is the interstitial tissue; it is only the tubules which show pigment granules, and these are contained in the epithelium of the convoluted tubes, but in greater abundance in the looped tubes. The granules are most common about the nucleus. If the jaundice last long, the inner layer of the capsule is coloured golden yellow, which Möbius thinks is due to the filling of the lymphatic vessels with pigment. The epithelium of the kidney becomes more and more filled with it, and the tubules themselves seem filled with pigment, so as to form casts of tubes formed of bile pigment. Möbius found no pigment in the kidneys in a case of phosphorus poisoning, acute yellow atrophy, or pyæmic jaundice.†

The other glands, the salivary and the pancreas, for example, show but little change. Neither do the sweat glands offer any striking morbid appearance. Frerichs says that now and then the contents of the tubule may appear somewhat yellow, and a few brown pigment granules be seen, but nothing more.‡

The skin as a rule shows after death no change in tint from that in life. If it be examined with the microscope, it is found to show in the lower layers, where the epidermal cells are youngest, the greatest amount of colour. In this it is like Addison's disease. The rounded cells, nearest the true skin, show brown and yellow granules about the nucleus.

† P. J. Möbius, *Arch. d. Heilkunde*, 1877. Jahrg. xviii. p. 83.

‡ Frerichs, *op. cit.* Bd. i. p. 109.

The mucous membranes which during life show but little of the yellow tinge, become much more coloured after death. Care must be taken in all cases of suspected jaundice not to make any diagnosis from the colour of the conjunctiva after death. This often assumes a distinctly yellow appearance, even where no jaundice or symptom of liver derangement was seen during life.

CHAPTER XIV.

THE FUNCTIONS OF THE LIVER IN JAUNDICE.

BUT little attention has been hitherto paid to the question whether the liver continue its functions in jaundice as in health. Indeed, it seems by some to have been assumed that the functions go on without interruption. The first intimation, since Claude Bernard's discoveries, that such a question was asked may be found in a paper by Kühne on jaundice. Benzoic acid, it is well known, is converted in the body into hippuric acid, probably by combining in the liver with glycocoll, in the presence of bile.* Kühne asserts that if benzoic acid be given to a jaundiced animal, no hippuric acid is seen in the urine, but the benzoic acid appears unaltered. This he thinks due to the liver's functions being altered in jaundice, so that no more free glycocoll or glycocholic acid is formed in the liver, but only taurocholic or cholalic acid.† Kühne's theory, however, was quickly made an end of; for several observers found that the disappearance of the hippuric acid was due rather to the decomposition of urine, and the reappearance of benzoic acid from putrefaction than to any other cause.‡

Golowin was the next, at the suggestion of Botkin, to raise any doubts as to the functions of the liver. From observations on jaundiced men and dogs, he came to the conclusion that the liver at the end of a long-continued jaundice lost the power of secreting bile acids.§ His observations will be spoken of again.

* Kühne and Hallwachs, *Arch. f. path. Anat.* 1857, Bd. xii. p. 386.

† Kühne, *ibid.* 1858, Bd. xiv. p. 320.

‡ See p. 293 of this work.

* Golowin, *Arch. f. path. Anat.* 1871, Bd. liii. p. 417.

* Skoda looks upon the view that the bile continues to be secreted in continued obstruction as venturesome, and that it is more probable that the pressure in the ducts causes a hindrance to the secretion of the cells. He even goes so far as to think that jaundice may be absent in complete obstruction to the ducts. Jaundice may decrease even if no bile pass into the intestine.* Very similar views are expressed by Jaccoud.†

The disturbing influence of jaundice upon the several functions of the liver will now be considered, each function being taken by itself.

i. The most important function of the liver known to us at the present day is the preparation of glycogen. This appeared to me so important a point to establish on a firm basis, that I have made a large number of observations upon animals in order to decide this point. In all cases I found that whether the animal died within a few hours or a few days after ligature of the bile ducts, in all cases alike, glycogen was absent from the liver. Glycogen was absent in all cases; it is not, therefore, merely the outcome of temporary disturbance due to the changes set up by the wound and other circumstances, but a permanent change in the function of the liver. The glycogen in no case returned again.‡ These observations have been confirmed by von Wittich,§ E. Külz, and E. Frerichs.|| In like manner, puncture of the fourth ventricle failed to cause sugar to be present in the urine a few days after ligature of the common duct.¶ It is evident, therefore, that in complete obstruction of the ducts the liver ceases to prepare glycogen.

* Skoda, Virchow and Hirsch's *Jahresbericht f.* 1868, Bd. ii. p. 142.

† Jaccoud, *Leçons de clinique méd.* (Lariboisière), Paris, 1873, p. 545.

‡ Wickham Legg, *S. Bartholomew's Hospital Reports*, 1873, Vol. ix. p. 161.

§ Von Wittich, *Centralblatt f. d. med. Wiss.* 1875. p. 291.

|| E. Külz and E. Frerichs, *Arch. f. d. ges. Phys.* 1876. Bd. xiii. p. 460.

¶ Wickham Legg, *Arch. f. exp. Path.* 1874. Bd. ii. p. 384.

It becomes a question now how far this fact in animals may be applied to jaundice in men, when there is sometimes evidence, from the presence of colour in the stools, that the obstruction to the ducts is not complete. In these and other cases, the phænomena seem best explained by supposing that the glycogenetic function of the liver is not altogether abolished, but rather impaired. Even in cases of simple jaundice the patient wastes and loses flesh rapidly, and this seems best explained by supposing a great impairment, if not destruction, of the glycogenetic function. Glycogen is always found in growing parts, and its importance to nutrition cannot be doubted.

The like absence of glycogen and sugar in the liver was found by Kütke in dogs in whom a biliary fistula had been established. The wasting which follows the setting-up of this flux is well-known.*

There is a case of Dr. Bright's, often quoted, of the concurrence of jaundice and diabetes. It is highly interesting. A man aged 49, of sober habits, became diabetic in March, 1827. At the beginning of September he became jaundiced, and by the end of December, the diabetes had disappeared. He died on March 1st, and the cause of death was found in a tumour of the pancreas, in which the dilated bile ducts terminated in a *cul de sac*.† Here the diabetes continued until it was put an end to by a permanent obstruction of the bile ducts.

ii. There is a second function of the liver, the secretion of bile. Now the important constituents of the bile are the pigment, the bile acids, and cholestearin. The amount of bile excreted by a healthy man has been very variously estimated. Let us take 10 grammes, the estimation of Westphalen,‡ so that the following figures

* Kütke, *Zur Function der Leber*, in Heynsius' *Stud. d. phys. Inst. zu Amsterdam*, Leipzig and Heidelberg, 1861. p. 52.

† Bright, *Med. Chir. Trans.* 1833. Vol. xviii. p. 3.

‡ See p. 105 of this work.

may be within the bounds of probability. Of these 10 grammes of dry bile, 5 must be made up of the soda salts of the bile acids, about one by mucus and pigment, and the remainder by cholestearin and the inorganic residues. Now if the liver in jaundice continue its functions of bile-making uninjured, there ought to pass out of the system daily, amounts of bile pigment and bile acids equivalent to these. The only secretion which has been hitherto found to contain them is the urine; and the urine therefore is to be examined with this view.

First as to the bile pigments. The urine is often deeply coloured, and its appearance would almost justify the belief that the same amount of the bile pigments which in health is passed into the duodenum must be contained in the urine. Yet Schwanda in his estimations found surprisingly little pigment. In the highest, the amount was only $\cdot 015$ grm. in the twenty-four hours. In others, $\cdot 014$, $\cdot 012$, $\cdot 011$, $\cdot 005$, and even $\cdot 002$, that is, only 2 milligrammes.* Thus the amount of pigment excreted by the urine is infinitely little when compared to the amount of pigment excreted by the liver in health. What is the reason of this difference? To me the best answer to this question seems to be that in jaundice the pigment-forming function of the liver is much injured. I am aware of the difficulties which this solution itself raises, but at present this theory seems to me best to explain facts.

Then as to the bile acids. The part which these play in the phænomena of jaundice has for some years past been a *crux* to pathologists. Formerly they could not be found in the urine, and there was great strife as to the cause of their absence. Now all agree that the

* Schwanda, *Wien. med. Wochenschrift*, 1865. p. 989. See above, p. 30. for the observations of Städeler on the great colouring powers of the bile pigment. A solution of one in a million was distinctly yellow in a two-inch layer.

bile acids are present in the urine ; but they are present in very small quantity. At the reckoning given above the liver ought daily to secrete at least five grammes of the bile acids. Now in jaundice, if we may believe what the chemists tell us, not so much as half a gramme passes out of the body daily by the urine. If the whole of the natural amount of the bile acids be secreted, what becomes of the remaining four and a half grammes? Ernst Bischoff, in answer to this question, imagines that the blood has the power of burning off so much of the bile acids, and no more ; that in jaundice more bile acids are taken into the blood than can be destroyed there, and that then the unconsumed excess is excreted by the kidneys.* He thinks there are only two hypotheses ; one, that the bile acids cannot be destroyed in the blood, and so do not pass into it in health ; or that in jaundice more bile passes into the blood than can be consumed therein. He hardly contemplates the possibility of the bile acids ceasing to be secreted in jaundice ; in fact he brings forward some reasoning and experiments which seem to show that all the sulphur of the bile acids which should be excreted *per anum*, passes out in jaundice through the urine.†

Leyden criticises Ernst Bischoff's theory by noting that even in slight cases of jaundice the bile acids may be found in the urine. If any quantity of the bile acids were burnt off in the blood, there would in such cases be no excess to appear in the urine. Also if bile acids

* Ernst Bischoff, *Zeitschrift f. rat. Med.* 1864. iii. Reihe, Bd. xxi. p. 144.

† He reasons thus: dry bile contains from '83 to 2'99 *per cent.* of sulphur: the mean is 1'5 *per cent.* Now taking 17 grm. as the amount of dry bile daily passing down the common duct (a low estimation) '3 grm. of sulphur are daily excreted. But the *feces* do not contain all this sulphur, part is absorbed and probably passes out in the urine: the amount of sulphur passed in health by stool is only '26 grm. Now in jaundice there is exactly '26 grm. of sulphur in the urine more than in health. Bischoff seems to suggest that the taurocholic acid is the source of this extra sulphur. (*op. cit.* p. 147.) This reasoning is open to many objections. It has been criticized by Leyden. (*op. cit.* p. 37.)

be injected under the skin of rabbits, they make their appearance in the urine, and the absorption is certainly very slow. And in these cases and in jaundice it is a long time before the bile acids entirely disappear from the urine. But it is very important that the resistance of the bile acids to chemical action should be borne in mind. They do not readily decompose even when added to putrid urine.*

There is, moreover, an objection at first sight to believing that the secretion of bile is unaltered in jaundice: it seems hardly likely that when the excretory duct of a gland is obstructed, the secretion into that duct should continue unchecked. Again Schiff thinks that a kind of circulation of bile between the liver and intestine goes on, and that when the supply of bile is cut off from the intestine, the amount of bile becomes much less.† Further, H. Huppert found that when the bile acids are injected into the blood, a considerable excess of bile acids is excreted by the liver in the bile.‡ It is thus possible that in jaundice the secretion of bile acids is much lessened, as no supply is drawn from the intestines, the gall duct being blocked up. Looking therefore at these facts just mentioned, the undoubted smallness of the amount of bile acids in the urine of jaundice and the intimate connexion between the bile-making function and the glycogenetic function,§ it would seem the most probable theory that in jaundice very little of the bile acids is secreted; and that, when

* Leyden, *Beiträge zur Pathologie des Icterus*, Berlin, 1866. p. 40.

† Schiff, *Arch. f. d. ges. Phys.* 1870. Bd. iii. p. 598.

‡ H. Huppert, *Arch. d. Heilkunde*, 1864, p. 244.

§ That there is an intimate connexion between the two can scarcely be doubted. Bernard found in the *Limax* that the liver alternately secreted bile and sugar. (*Leçons sur les propriétés physiologiques et les altérations pathologiques des liquides de l'organisme*, Paris. 1859. t. ii. p. 203.) It is probable also that albuminous matters are broken up in the liver, the carbon, hydrogen, and oxygen, going to form glycogen, while the refuse of this process, the carbon, hydrogen, oxygen, sulphur and nitrogen, forms the bile acids.

the jaundice is of long standing, and the glycogenetic function completely abolished, the bile acids likewise cease to be secreted, as the observations of Golowin and others teach.*

What is now wanted are more and accurate estimations of the amount of bile acids passed in the urine of jaundice. Some may doubt if the amount of bile acids have ever been accurately estimated; but there is no good reason for denying that the amount is very small; and the quantity given above, half a gramme, is far higher than that given by any observer who has estimated them.

It may well be asked: why, if the secretion of bile be entirely stopped, do the skin and urine become so coloured? To this it may be answered: it is not affirmed that the secretion of bile is entirely suppressed; witness the presence of the bile acids and bile pigment in the urine, though in small quantity; and if a small quantity of bile pigment only be secreted, it would be enough to colour the skin and urine. The yellow colour which is common in jaundice is indeed an argument in favour of the secretion being suppressed; for if the whole amount of pigment, natural in health, continued to be secreted, the skin of every jaundiced European would resemble a negro. That there is a decrease of the amount of pigment is attested by Dr. Budd who says: "It sometimes happens that after complete closure of the common duct has existed many months, and while no bile flows through it into the intestine, the jaundice of the skin becomes very much less deep, and the urine very much less deeply stained with bile. I have, indeed, more than once known the jaundice gradually diminish and almost entirely disappear after the lapse of twelve months, to the great satisfaction of the patient, although the colour of the intestinal discharges

* See the section on the urine, p. 286 of this work.

and an examination of the body after death, showed that the closure of the duct was still complete."* Dr. Murchison has some remarks to the same effect.†

iii. A third important function of the liver is the maintenance of animal heat. For the discovery of this important office we are again indebted to Claude Bernard. He found that the temperature of the blood coming from the hepatic veins was higher than that of any other part of the body.‡ The high temperature is clearly due to the active chemical processes which go on in the liver, the oxydations connected with the formation of glycogen, of bile, and with the process of sanguification. If the arguments used in the foregoing paragraphs be at all sound, it should follow that, in obstruction to the ducts of the liver, and consequent abolition of two important functions, the temperature of this organ should fall, and with it the temperature of the whole of the body. It is notorious that the temperature in jaundice is almost always below the natural standard; and that even in those cases where a pyrexial complication is present, the temperature never rises so high as is customary in uncomplicated disorders.

While passing through Lyons after the Easter of 1878 I had an opportunity, thanks to the courtesy of M. Chauveau, of making some experiments directed to this point. The bile ducts of dogs were ligatured, and forty-eight hours after the ligature of the ducts, the temperature in the upper part of the inferior cava was ascertained, by means of a thermometer passed through the jugular and right auricle. It was found, however, that a traumatic pyrexia had been set up, and the temperature of the vena cava and of the rectum was in all

* Budd, *On Diseases of the Liver*, London, 1857. p. 231.

† Murchison, *Clinical Lectures on Diseases of the Liver*, London, 1868. p. 427.

‡ Bernard, *Leçons sur les propriétés physiologiques et les altérations pathologiques des liquides de l'organisme*, Paris, 1859. t. i. p. 85.

cases equal. It would be necessary, in any other series of experiments, to wait until the pyrexia had gone down. This, again, involves a risk, as the animals are not likely to survive the operation many days.

iv. There is said to be another function of the liver, to which allusion has already been made; that of sanguification. C. G. Lehmann found the blood of the hepatic vein to contain a far greater number of red and colourless corpuscles than that of the portal vein. The number of the colourless corpuscles is also increased relatively to the red. The red are distinctly violet in colour, and they resist the action of water upon them.* He also says that the red corpuscles are smaller, and less regularly lenticular.† The blood of the portal vein also shows fibrin in no way different from that of the rest of the body: but the blood from the hepatic vein can hardly be got to clot at all, and when whipped, shows only a few threads of fibrin. The extractives and fats are also in greater quantity in the hepatic vein than in the portal.‡

Ernst Hirt confirms Lehmann's statement as to the increase of the white corpuscles; he finds that the number of white corpuscles to the red in the blood of the portal vein is about 1 to 700 or 750, while in the hepatic vein the number is about 1 in 68 or 274.§

Dr. McDonnell, so well known from the numerous observations which he has made on the functions of the liver, affirms without hesitation that the blood of the hepatic veins of dogs is not capable of coagulating spontaneously, and that it does not give fibrin on being whipped, and that the hepatic blood contains colour-

* C. G. Lehmann, *Physiological Chemistry*, Cavendish Soc. ed. Vol. ii. p. 259.

† Idem, *Journal de Pharmacie et de Chimie*, 1852. t. xxi. p. 396.

‡ Idem, *Comptes rendus*, 1855. t. xl. p. 585. The absence of coagulation in the blood of the hepatic vein has also been noted by Brown-Séquard. (*Journal de la Physiologie*, 1858. t. i. p. 298.)

§ Ernst Hirt, *Müller's Archiv. f. Anat. Phys.* 1856. p. 191.

less corpuscles five to ten times more numerous than in the portal blood.*

Flügge, comparing analyses of the blood of the portal and hepatic vein, has come to the conclusion that there is but little difference between the blood in these two vessels. He found the amount of the solids, nitrogen, phosphates, and chlorides, almost the same in both, and the amount of hæmoglobin about equal. So that if Flügge's observations and his method may be trusted, great doubts will be thrown upon the functions of the liver as a blood-making organ.†

Drosdoff, however, has made analyses of the blood of the portal and hepatic veins in Hoppe-Seyler's laboratory in Strassburg, and sharply criticises Flügge's methods. Drosdoff finds that the solids of the portal vein are always greater than those of the hepatic, and that the hepatic vein is always richer in cholestearin and lecithin than the portal vein, while the reverse holds good about fats.‡

There are many analyses and observations which show that in jaundice the amount of red corpuscles is much decreased.§ Budd attributes this not so much to the mere presence of the principles of the bile in the blood, as to the diminution of those reparative changes which the blood naturally undergoes in its passage through the liver, and on the absence of bile in the intestines.|| I feel disposed to agree with Budd rather than with Leyden, who thinks that the pooriness of the blood is due to the action of the bile acids upon the blood corpuscles.¶ For if, as in the foregoing para-

* McDonnell, *Observations on the functions of the Liver*, Dublin, 1865. pp. 28 and 38.

† Flügge, *Zeitschrift f. Biologie*, 1877. Bd. xiii. p. 133.

‡ W. Drosdoff, *Zeitschrift f. phys. Chemie*, 1877. Bd. i. p. 233.

§ See the section on the blood in jaundice, p. 269.

|| Budd, *On Diseases of the Liver*, London, 1857. Third Edition, p. 468.

¶ Leyden, *Beiträge zur Pathologie des Icterus*, Berlin, 1866. p. 118.

graph upon the secretion of the bile I have endeavoured to show, the whole amount of bile acids poured into the circulation daily be less than half a gramme, the action of the bile acids upon the corpuscles must be extremely small, since the bile acids will be in so dilute a solution that they can scarcely be thought to act on the corpuscles.

CHAPTER XV.

THE DIAGNOSIS AND PROGNOSIS OF JAUNDICE.

Diagnosis. The diagnosis of jaundice is commonly a matter of extreme ease. All that is necessary is to look at the patient's face, and especially the conjunctiva, by daylight. To confirm this observation it is often desirable to ascertain the presence of bile pigment in the urine, and the absence of colour in the fæces.

There is one discoloration of the face very liable at a superficial glance to be mistaken for jaundice, and that is the yellowness caused by exposure to the sun. It is seen, of course, chiefly in men, but the conjunctivæ remain colourless, and the urine free from bile pigment. Further, the parts covered by clothing are of the natural white.

The same pearly whiteness of the conjunctiva, and absence of the bile pigment from the urine distinguish chlorosis, in which the skin is often of a yellowish tinge, the cachexia of cancer, lead poisoning, and agues. It seems unlikely that the pigmentation of the skin in Addison's disease should be mistaken for jaundice; and some assert that the yellowness of the new-born is shown not to be a jaundice by the absence of colour from the conjunctivæ and of bile pigment from the urine.

In some persons a layer of fat lies immediately under the conjunctiva, and it is necessary to add a caution to the young practitioner, not to be deceived by this, as it causes a yellow appearance liable to be mistaken for slight jaundice. It will be known because the yellow colour is not present everywhere in the conjunctiva, but only in those parts of the sclerotic where the fat is most abundant.

Jaundice may be feigned by soldiers, sailors, and prisoners, for their own purposes. It is done by staining the skin with any yellow pigment: infusions of saffron, turmeric, and the like are said to be those most commonly employed. Such deception may be easily detected, as the conjunctivæ remained uncoloured; and a little soap and water, or chlorine water, or chloride of lime, will discharge the colour of the skin. If their cunning have gone the length of taking rhubarb or santonin for the purpose of darkening the urine, the urine will be deepened to a red by alkalies, whereas the urine of true jaundice is coloured brown. Further, there will be no reaction with nitric acid.

A far better means for deceiving the physician would be the carbazotate or picrate of potash taken internally. This is said to stain the skin and tissues of a fine yellow, but the urine does not contain bile pigment, nor are the stools colourless.

Nothing can be easier than to say that a patient is jaundiced; but it is often one of the most difficult problems in medicine to point out the cause of the jaundice. It is sometimes hard even to approach a diagnosis, nothing but a guess being possible; and it is not often that the physician can feel very great confidence in the opinion which he puts forth. A few suggestions are added upon the lines of which the clinical physician may work in his search after the causes of jaundice.

First, it is of considerable importance to be able to feel the distended gall-bladder at the lower border of the right lobe. If this can be distinctly felt and percussed out, much information is gained. The cause of the jaundice will in all likelihood be below the junction of the cystic and hepatic ducts, in fact, in the common duct. In cases where the jaundice is due to changes in the liver itself the gall-bladder is very often empty or only half filled, and cannot therefore be felt.

Next, the state of the stools must be looked into, whether they be altogether or but partly free from colour. It may be thought by some that a complete absence of colour in the stools is a sign of complete obstruction of the duct.

i. Should the jaundice be recent and no perceptible disease be found in the liver or elsewhere, the case is probably one of simple jaundice.

ii. The jaundice being recent but acute disease of other parts present: such as pneumonia, pyæmia, typhoid and relapsing fevers, and the like, delirium tremens, poisoning by chloroform, chloral hydrate and other drugs, and snake-bites, the cause of the jaundice is not known with any certainty; but it is probably the same as in simple jaundice.

iii. If the jaundice be accompanied or preceded by attacks of severe shooting pains in the right hypochondrium; or if the jaundice be intermittent, one attack quickly succeeding the other, the cause is probably gall-stones.

iv. An intense persistent jaundice, if approaching twelve months in duration, is due, probably not to cancer, but to gall-stones, hydatids, or stricture of the duct.

v. A slight persistent jaundice is probably due to changes in the texture of the liver, as cirrhosis, nutmeg liver, &c.

vi. Jaundice with great enlargement of the liver is probably due to cancer.

vii. Jaundice complicated with ascites is probably due to cirrhosis.

viii. Delirium setting in during an acute jaundice suggests *icterus gravis*.

Prognosis. The length of time which a jaundice may last varies with the cause of the jaundice. In one case, the yellowness may be a mere transitory symptom, last-

ing but a few days, the conjunctiva only being coloured, and the urine just showing a faint reaction of bile pigment. In another, the jaundice may be intense and last three or four years. Or the patient may recover from one attack, only on recovery to fall into another access of the same disease, and this alternation of health and disease may last many months, or even years. Such a case is reported by Van Swieten, in which a woman had jaundice off and on for 12 years.* Heberden says he has known the jaundice return frequently for more than 20 years in some persons, who have had good health in the intervals of the fits. He also speaks of a woman who for five years laboured under all the usual symptoms of the jaundice in the highest degree.† Dr. Joseph Ayre speaks of a gentleman who had been jaundiced for eight years from a permanent obstruction of the biliary duct,‡ and Devay of a woman who stated that she had been jaundiced for 7 years.§ She was only under observation a few days before death; a peasant, and of "*intelligence faible et grossière*," so that but little trust can be placed in her statements. I have myself seen a patient jaundiced continuously for six years and a half, and yet able to do light work, such as book-keeping or account keeping.

How long may a patient live with the gall ducts completely obstructed? Graves and Stokes have recorded a case of jaundice in which the stools were colourless for two years, yet the appetite returned, the bowels became regular, and all bad symptoms disappeared.|| Dr. Hilton Fagge speaks of a case lasting 7 years with

* Van Swieten, *Comment.* § 950, Lugd. Batav. 1755, t. iii. p. 130. This case is usually quoted as if the jaundice had persisted for 12 years without intermission. It was continuous only for the last of the twelve years.

† Heberden, *Commentaries*, Lond. 1806, Third ed. p. 243.

‡ Joseph Ayre, *Practical Observations on those Diseases of the Liver, etc.* Lond 1821, p. 16.

§ Devay, *Gaz. méd. de Paris*, 1843, p. 263.

|| Graves and Stokes, *Dublin Hospital Reports*, 1830. Vol. v. p. 109.

persistent jaundice.* But there is every reason to think that a case of complete obstruction to the gall ducts rarely lasts for more than a twelve-month. Very few of my own cases have lasted so long. The matter is of course different when the obstruction is incomplete, or the jaundice intermitting.† Much also, in the length of time which jaundice will last, depends upon the nature of the obstruction. Jaundice caused by cancer will, in the usual course of events, end more quickly than that caused by hydatids, gall stones, or other permanent constriction of the duct.

The prognosis of jaundice depends solely on the cause. If due to organic disease of the liver, the prognosis becomes involved in the liver disease. If, as in so many cases of simple jaundice, there be no apparent disease of the liver, the prognosis becomes exceedingly favourable; the immense majority of cases of simple jaundice end in six weeks in the complete recovery of health. Still, the practitioner can never feel quite happy even when attending the simplest case of jaundice, as the beginnings of acute yellow atrophy cannot in the present state of knowledge be distinguished from simple jaundice. The physician should thus be on his guard not to give too confident a prognosis, lest in a few days delirium or coma come on, and his forecast falsified.

The appearance of nervous symptoms or of hæmorrhages, whether in acute or chronic jaundice, is certainly of very evil augury, and is most commonly the forerunner of death. The same may be said of a rise of temperature. The slow pulse is usually without influence on the prognosis; Karl Kétli has, however,

* Hilton Fagge, *Guy's Hospital Reports*, 1875. Vol. xx. Third series, p. 164.

† Hertz has published (*Berlin. klin. Wochenschrift*, 1877, p. 76) a case with details rather obscurely related in which the same intermitting jaundice was noticed from Christmas, 1871 to death in April, 1874. It would seem, but this is not at all clear, that the jaundice was persistent the last two years before death.

published a case of jaundice in which death seemed to take place from the heart; the pulse became slower and slower, until the patient died.* Itching and xanthelasma have no influence on the prognosis. Xanthopsia and nyctalopia are thought by some to be very bad signs.

The best symptom that can be seen in jaundice is a return of colour in the stools. This symptom appears first of all, long before the yellow colour has begun to disappear from the conjunctiva, or the urine to lose its pigment: indeed the urine, as it is the first to show the pigment, so it is often the last to lose it. Care must be taken in judging of the stools to be sure that the colour is due to bile, and not to a foreign admixture.

* Karl Kétli, *Wien. med. Wochenschrift*, 1878. p. 135.

CHAPTER XVI.

THE TREATMENT OF JAUNDICE.

JAUNDICE is but a symptom ; and in its treatment, attention must be first of all paid to the causes which bring about the jaundice. If the jaundice be associated with a gastro-duodenal catarrh, this state of the mucous membrane must first be remedied. If the jaundice be due to the pressure upon the gall duct of hardened fæces in the large intestine, these should be removed. Or if due to the passage of gall stones, the main aim of the physician will be to render the escape of the gall stone from the common duct more easy. If tumours outside the liver, and these may spring from any neighbouring organ, press on the gall ducts, an attempt should be made to relieve the pressure. In jaundice from disease of the liver, the disease of the liver itself should be treated, and the jaundice may almost be neglected. Thus the treatment of jaundice resolves itself into the treatment of the disease causing the jaundice, and to this the judicious practitioner will commonly restrict himself.

But though the treatment of jaundice should be left to that of the disease by which it is caused, yet the results of the jaundice, the injuries done to the functions of the liver, and the consequent damage to the general health, deserve some attention. The means at our disposal for the relief of these states are but feeble, as it would be folly to expect that the effect would cease while the cause is in active operation.

First, the supposed injury to the digestion in the intestines from the lack of bile may be considered. It is doubtful, however, if bile be of any importance, save for

the digestion of the fats; and seeing this, fat should be carefully excluded from the diet of the patient, if he do not instinctively shun it. To remedy the want of bile in the intestine, it was proposed many years ago by Eaglesfield Smith to give the bile of animals to patients suffering from jaundice,* and in the present day, ox-bile is given, enclosed in capsules, nicely regulated, it is said, to break at the moment of passing the pylorus. Setting aside the question whether they do indeed melt at the right moment, or whether they do not beforehand discharge their contents in the stomach, and thus upset the process of gastric digestion, experience does not give a very favourable account of their method. I have seen the capsules employed, and I do not think I have noted any marked benefit follow their use. Indeed, it was hardly to be looked for.

Secondly, the damage done to the liver itself. Physiologists are not acquainted with any means for artificially supplying glycogen; nor do therapeutists know any remedy by which the overgrowth of connective tissue in the liver may be checked. But some attempt may be made to stay the wasting and anæmia which are associated with the hindrance to the flow of bile into the duodenum. Attention to the nutrition of the patient formed a large part of the treatment of Hippocrates.† Fatty foods, it has been said, are improper; and thus cod-liver oil should be excluded. Nitrogenous aliments should be chiefly used; such as lean beef or mutton. Some writers represent patients with jaundice as suffering from much flatulence; and when this is the case, it would certainly be proper to abstain from food containing starch and sugar. If no inconvenience be felt from wind, this kind of food would be desirable, when the direct supply of fat is taken away.

* See above, p. 135.

† Hippocrates, *de locis in homine*, Cap. xxviii. Littré's ed. t. vi. p. 320.

The impoverishment of the blood should be met by giving some of the neutral preparations of iron, such as the reduced iron; or the old steel wine, prepared from iron filings; or Squire's chloroxyde. Sometimes the patient may with benefit be sent to a chalybeate spring; advice given by Sydenham two hundred years ago.*

It has been already stated that the great channel by which the bile pigment and bile acids leave the blood is the urine. By the skin only a very small amount is excreted; by the other glands, nothing. In many cases of jaundice, the amount of urine is much increased, and it is desirable to keep up an increased flow of urine, a plain indication of nature, by means of drugs.† The neutral salts of potash and soda, especially the citrates and acetates, will be found useful, aided by the mineral waters commonly used as drinks, such as Seltzer, or Apollinaris. Frerichs recommends lemon juice, one and a half to three ounces daily, and says it has the advantage of both aiding digestion and causing an abundant diuresis.‡

The activity of the skin should be favoured by warm clothes and warm rooms, especially as the temperature of the body is often low. Of the action of Turkish baths in jaundice I have unfortunately no experience. They are likely to further the excretion of the colouring matters by the skin, and at the end of the disease to favour the disappearance of the yellow colour. It is, when the obstruction to the ducts has been removed, that the skin and kidneys may most advantageously be stimulated; and at the same time excretion of bile may be increased by doses of the alkaline benzoates.§

* Sydenham, *Processus Integri*, Cap. xxix. in *Opera omnia*, ed. Greenhill, p. 583.

† Warm baths and diuretics formed great part of the Hippocratic treatment of jaundice. (*Op. cit.* pp. 244 and 320.) Graves hints rather obscurely at the use of diuretics. (*Clinical Lectures*, Dublin, 1864. p. 633.)

‡ Frerichs, *Klinik d. Leberkrankheiten*, Braunschweig, 1858. Bd. i. p. 129.

§ Benzoic acid was recommended by C. Ph. Falck of Marburg in cases of

These salts are said to rapidly clear the skin of colouring matters.

Besides the rational treatment of jaundice, there are other, empirical methods, which have been employed from the earliest times, and of which it is now necessary to speak. Amongst these stand purgatives and emetics, acids and alkalies, and substances supposed to have a direct action on the liver, such as the juice of certain plants. Some of these empirical methods of treatment are identical with those which we call rational.

i. Purgatives have long enjoyed a great reputation. Calomel used formerly to be given in all cases of jaundice, and physicians were not content with giving it merely as a purgative occasionally, but it was almost a routine practice to give mercury so as to affect the mouth, and to bring on salivation. This has doubtless caused it to lose its reputation, as well as the evidence lately offered that it has no specific action on the flow of bile into the intestine. Podophyllin, which is called the vegetable mercury, has, it is said, a more active influence upon the secretion of bile; but for this very reason it seems to me undesirable to be used in cases of obstruction to the ducts, or disease of the liver.*

Other purgatives, besides mercury and podophyllin, were used, such as jalap and cream of tartar, sulphate of magnesia, aloes, and colocynth. Or the patient was sent to drink the purging waters at Harrogate, Cheltenham, Friedrichshall or Püllna. I should, however, long hesitate before I subjected a patient with a chronic jaundice to a course of purgative

jaundice and liver disease. (*Corr. Bltt. d. Ver. f. gemeinsch. Arb.* No. 30. reported in Canstatt's *Jahresbericht f.* 1858. Bd. v. p. 126.) Justi used it with good success in the jaundice of children (*ibid.* No. 31.) but it should be remembered that the jaundice of children usually runs a very favourable course.

* See the chapter on the Action of Drugs upon the Secretion of the Bile, pp. 157, 174 and 178.

medicines. One purgative dose may be given early in the treatment, or perhaps when the bowels become costive; but a series of purgings will lower the patient's strength, or even do him a serious damage.

ii. Emetics were once greatly in vogue for the cure of the jaundice.* By the act of vomiting, the liver and gall-bladder are pressed upon from three sides, and it was thus thought that the bile would be forced out into the duodenum through any moderate obstruction. This may possibly be the case if the obstruction be nothing but a plug of mucus; for it may be seen after death how slight a pressure on the gall bladder will suffice to send the bile into the duodenum. Still, the diagnosis must have attained a high degree of certainty for such violent remedies as emetics to be indicated; for, if the obstruction be a solid tumour pressing on the ducts, or a cancerous head of the pancreas, or a large gall stone firmly impacted in the ducts, an emetic is more likely to cause a rupture of the gall bladder or ducts than a resolution of the obstruction.

If the foregoing be a correct account of the action of emetics in jaundice, it is clear that they are worse than useless in all cases of jaundice from disease of the liver or where the obstruction in the large ducts is of a permanent kind. The cases in which emetics may be most serviceable are those of jaundice caused by a plug of mucus, or a small easily-moved gall stone.

The tartar emetic has been much lauded. Frerichs says that he found the bile passages of dogs to whom he had given tartar emetic empty and perfectly free from bile.† Still tartar emetic cannot be recommended in cases of acute catarrh of the stomach. It is well known that antimony and its congeners cause a catarrh

* Hippocrates recommends them. (*De affect. inter.* Cap. xxxv. Littré's ed. t. vii. p. 254.)

† Frerichs, *op. cit.* Bd. i. p. 131.

and fatty degeneration of the tubular glands of the stomach: and it would seem unwise to prescribe a drug which has the power of begetting the same disease as that from which the patient already suffers. Ipecacuanha has also been recommended, and if emetics be determined upon it would seem preferable to antimony. Sir Dominic Corrigan recommends it in 30 grain doses every other day.*

It would need much stronger evidence as to the value of emetics in jaundice than at present exists, to persuade me to recommend a course of such treatment to a patient suffering even from simple jaundice.†

iii. Acids, both mineral and vegetable, have long enjoyed a great reputation in the treatment of jaundice; and they may be used without fear of any of the ill effects which sometimes accompany emetics and purgatives. Heberden says he has known large quantities of acid, such as lemon juice, gain the credit of the cure of jaundice;‡ and Scott praises the nitro-muriatic acid given by the mouth or used in the bath.§ For this latter purpose I can hardly recommend it; but I think I have seen good follow doses of ten or twenty minims of the dilute acid three times a-day. The action of the acid is explained in different ways. Some think that *aqua regia* has a specific action upon the liver, and appeal to Dr. Rutherford's observation: others think that acids act by irritating the duodenal papilla as in Claude Bernard's well-known experiment.||

iv. The alkaline carbonates and soaps were formerly given, to make amends for the deficiency of the bile, by aiding the digestion and cleansing the bowels.¶ At the

* Corrigan, *Dublin Hosp. Gaz.* 1845, pp. 69 and 71.

† Stoll condemns the use of emetics in jaundice and says he has seen much harm from them. (*Rat. Med.* pars iii. Viennæ, 1780, p. 388.)

‡ Heberden, *Commentaries*, London, 1806, Third ed. p. 259.

§ H. Scott, *Med. Chir. Trans.* 1817, Vol. viii. p. 173.

|| See pp. 127 and 173 of this work.

¶ Heberden, *loc. cit.*

present day they are most commonly administered in the Carlsbad and Marienbad waters. With these, it must be remembered, a large amount of water is taken, as well as other salts besides carbonates, but they sometimes relieve cases in which other remedies had been unsuccessful.

In the early stages of a jaundice complicated with gastric catarrh, a mild alkaline course is often most useful.

v. Simples have enjoyed a great reputation, the foundation of which is thought to have been laid by Van Swieten. He treated a woman, 60 years old, who had been troubled with the jaundice for 12 years, after the following plan: the juice of grass, milk whey, and the like during the spring; the Spa waters during the summer; and Venice soap and honey during the winter. For six months she had a coeliac flux, and passed abundance of small stones, with recovery.* In like manner the juice of the *taraxacum* and of the *carduus benedictus*, especially if freshly expressed, has been much lauded, chiefly by village practitioners.† There is, however, very little evidence of the value of these herbs in the treatment of jaundice.

Conium, belladonna, and other anti-spasmodics, were much used in the treatment of jaundice when it was thought that the symptom depended on spasm of the gall ducts; and with the revival of a doctrine of *icterus spasticus* may come again into fashion.

* G. van Swieten, *Comment.* § 950. Lugd. Batav. 1755, t. iii. p. 130.

† Some of the remedies for the jaundice used by the public, and which have in a few instances made their way into pseudo-therapeutic works, are more interesting to the student of folk lore than to the physician. Such are the administration of spiders and lice; the mixing of urine with honey and sugar; (Cf. Pliny, *Nat. Hist.* Lib. xxx. Cap. xi.) making a cake with the urine of the patient and meal, and giving it to a dog, who must be of the male sex; or the more loathsome suggestion of dosing the patient with the excrements of the goose; a plan of treatment which I believe the homœopaths have made their own, and in the possession of which no one is likely to disturb them.

With Bamberger,* we may regret that not a step has been made forward in the treatment of jaundice for 2000 years, and that the therapeutics of this age are, in all essential points, the same as those of Hippocrates and the early Greeks.

Treatment of the Complications of Jaundice. The wasting has already been spoken of. The patients are often chilly, and complain of a sensation of cold: this may best be treated by attention to the clothing, which should be a matter of care in nearly all cases of jaundice. The high temperature which comes on just before the fatal ending of the case should not, in my opinion, be treated.

The itching of the skin is sometimes so severe that narcotics must be given to procure sleep. I have myself seen the most relief from mercurial ointments, made with calomel or white precipitate. Sometimes spirituous lotions, containing hydrocyanic acid, or carbolic acid and glycerine, give ease. The warm bath with friction may also be employed.

The slow pulse and changes in the senses do not need special treatment.

The setting in of hæmorrhages is of bad omen, and little can be done by way of treatment.

Gallic acid and tannic acid may be used internally and externally; or large doses of the tincture of iron, or turpentine may be given. If the bleeding be from the nose, and very abundant, it would be right to plug the nares.

Like the hæmorrhages, the appearance of nervous symptoms is a bad sign. I have seen advantage in these cases from active purging; but severe treatment such as blisters to the head or nape of the neck, leeches, hourly doses of calomel, and the like, cannot be recommended.

The xanthelasma should remain untreated.

* Bamberger, *Krankheiten des chylopoët. Systems*, Erlangen, 1864, p. 484.

CHAPTER XVII.

ICTERUS SIMPLEX.

SYNONYMS. *Icterus communis, benignus, catarrhalis, gastroduodenalis, duodenalis, spasmodicus, spasticus, vernalis.*

Simple jaundice is a mild disorder which runs a quick course towards recovery, and which shows no signs of any notable disease in any organ, even in the liver itself.

This jaundice has been known and described from the earliest times, but it cannot be said that its nature and cause are even now beyond a doubt.

It is by far the most common of all the varieties of jaundice; it is probable that it is oftener seen than all the other varieties added together.

A surfeit of food, especially if indigestible, and, above all, a fit of drunkenness, are apt to be followed by a gastric catarrh and a jaundice. In these cases the ætiology of the jaundice would be said by many to be clear. In some the vomiting may come on after exposure to bad smells,* or other unwholesome influences, as is well seen in cases of simple jaundice, which, when numerous enough, are called epidemic jaundice, but are not uncommonly seen in single cases. Then there is a jaundice which follows mental emotions of all sorts, the old *icterus ex motu animi*. This cause of jaundice is said to be so firmly held by the vulgar in Germany that all cases are unhesitatingly set down to mental emo-

* Powell (*Observations on the Bile and its Diseases*, Lond. 1800. p. 77) says that medical students are often seized with the jaundice soon after they begin to work in the dissecting room. Powell seems to attribute this to the posture and confinement necessary for this study. I have not myself observed medical students to be more often jaundiced than others; but if it were a fact, I should attribute it rather to the bad sanitary state, as I have often seen persons exposed to bad smells and the like, jaundiced.

tion.* In the older writers there will be found many cases of jaundice immediately following great mental emotion;† there are cases of prisoners becoming yellow at the moment that sentence of death was pronounced upon them; of two young men about to fight a duel, when one of them saw the other become so yellow, that being astonished, he ceased to fight; of a young priest, frightened by a dog, falling half dead, and being taken up yellow as saffron: of a young soldier, who, being struck in a public place, attempted to return the blow, but, being hindered by the bystanders, became jaundiced almost at that instant, and soon after fell into a fever and delirium, and died in the midst of convulsions.‡ All these cases seem to me capable of quite a different interpretation; the pallor caused by excessive fear is often yellowish; and may have been easily mistaken by inexperienced or careless observers for a true jaundice.§ In none of the cases does a careful examination seem to have been made; nothing is

* Frerichs, *Klinik d. Leberkrankheiten*, Braunschweig, 1858. Bd. i. p. 166 note. The same notion prevailed in England; as Shakspeare can testify:

"Creep into the jaundice
by being peevish."
Merchant of Venice, I. i.

"What grief hath set the jaundice on your cheeks?"
Troilus and Cressida, I. iii.

† I do not think that Horace meant to speak of jaundice when he describes the following effect of jealousy:

Quum tu, Lydia, Telephi
Cervicem roseam, cerea Teleph
Laudas brachia, vae meum
Fervens difficili bile tumet jecur.

(*Carm. Lib. i. Od. xiii.*) The poets contain many allusions to the liver, as it was the seat of the emotions, love, courage, &c.

‡ Portal, *Observations sur la nature et le traitement des maladies du foie*, Paris, 1813. p. 141.

Villeneuve, *Dict. des Sciences méd.* Paris, 1818. t. xxiii. p. 419.

§ The jaundice described by Sydenham (*Obs. Med.* iv. 7. Greenhill's ed. p. 202) as seen in hypochondriac men and hysterical women, must, I venture to think, be put down to gall stones rather than a nervous affection. In this opinion Heberden shares: "No reasonable deference to this accurate observer can make anyone much doubt of his having been mistaken." (*Comm. Lond.* 1806. Third ed. p. 240.)

said about the conjunctiva or the state of the urine. It is, however, otherwise with the cases in which an interval, of days or weeks perhaps, comes between the emotion and the appearance of the jaundice. To these credence may be given, though whether the emotion be a cause of the jaundice remains to be discussed. Some of these cases are quite classical, and are quoted everywhere.*

Sir Thomas Watson† and Dr. Bence Jones‡ supported the theory that mental emotion was a cause of jaundice.

In certain cases no cause whatever can be discovered. The season of the year has some influence; simple jaundice is more common in the spring and fall, particularly the autumn.

In simple jaundice, the first notice that the patient is ill is often the sight of his own face in the glass, or the being told by others of his yellow colour. This may happen on rising in the morning, and the patient then finds that he has lost appetite and feels sick; or he may even vomit. In a certain number of cases, the gastric symptoms come on later, even three or four days after the jaundice. In other cases, the greater number, perhaps, the gastric symptoms appear before the jaundice, a day, a week, or even longer.

When the gastric symptoms are not marked, there are sometimes signs of an intestinal catarrh, diarrhœa, or tape worm, and the like.

* Dr. Wilks has recorded a case of jaundice which he appears to think due to emotion, the patient having been much frightened five days before the jaundice came on. There were, however, at the same time, headache, nausea, and slight diarrhœa. (*Brit. Med. Journal*, 1870. Vol. ii. p. 4.) In the same volume (p. 547) Mr. Churton has published a case in which "acute hepatic pain" and mental disturbance came together. The jaundice was treated with bromide of potassium, and recovery seems to be attributed to the use of this remedy. Dr. A. W. Foot (*Dublin Journal of Med. Science*, 1874. Vol. lvii. p. 217) and Ferber (*Arch. d. Heilkunde*, 1868. p. 558) have also published cases which they set down to emotional causes.

† Sir Thomas Watson, *Lectures on the Principles and Practice of Physic*, Lond. 1857. 4th ed. vol. ii. p. 609.

‡ Bence Jones, *S. George's Hosp. Reports*, 1866. vol. i. p. 193.

Frerichs found that out of 41 cases of simple jaundice symptoms of a gastro-intestinal catarrh were present as *prodroma* in 34.* In my own cases, the proportion is nothing so great; but my figures, I must own, prove little or nothing. They were taken from out-patients; and many of the cases I saw only twice or three times, so that I was unable to verify my diagnosis by seeing the recovery of the patient.

It must be owned that in certain cases, no other symptom save that of jaundice can be found out. The patient says that he is in good health, saving only his yellow appearance, and applies for medical help purely on account of his yellow colour.

With the gastric symptoms there commonly set in, especially with women, giddiness, headache, and a sense of weakness or feebleness, which may be so great that a febrile disorder may be thought of, typhoid or the like. There is not unfrequently a slight rise in the temperature, which rarely passes above 100°. The tongue is usually coated with a white fur; there may be diarrhœa or constipation, and the fæces are colourless. The pulse usually preserves its natural number of beats. In women it may even be a little quicker; in some cases it becomes slow, as 60 or 65; and in rare cases it may sink lower, even to 40. Itching is often seen; xanthopsy rarely.

On physical examination, the liver will as a rule be found slightly enlarged, and the right hypochondriac and epigastric regions somewhat tender to pressure. Gerhardt has pointed out the importance of being able to feel or percuss the enlarged gall bladder,† this, however, is not always possible; as the shape and position of the reservoir are not constant. When made

* Frerichs, *Klinik d. Leberkrankheiten*, Braunschweig, 1861. Bd. ii. p. 418.

† Gerhardt, *Ueber Icterus gastro-duodenalis*, in Volkmann's *Sammlung klinischer Vorträge*, Leipzig, 1870-75, p. 107.

out, it is an important sign of obstruction to the common duct.

Bamberger states that pulmonary catarrh is very often an accompaniment of this simple jaundice.*

A simple jaundice always ends in recovery, and the first sign of convalescence is said to be a return of the appetite. Bamberger notes during convalescence a *fames canina* like that seen after typhoid.

The disease may last as short a time as a week or ten days; or be prolonged to three and even four months. After two months, great suspicion must rest on the diagnosis. The average appears to be three to four weeks.

As the disease never ends in death, but always in recovery, there are no opportunities for examining the cause of the jaundice by the help of anatomy, unless the life of the patient be ended by accident or some other disease; in this last case the observation will not be quite free from suspicion. The cause of the jaundice therefore remains unknown, and it is only by a comparison with like diseases and states, that any light can be thrown on the matter.

One point only is tolerably certain; that the bile does not find its way into the duodenum, as shown by the colourless state of the stools; and in those cases in which the gall bladder is found distended, it may be asserted that the hindrance is in the common duct. All beyond this is little better than conjecture.

The conjecture which found greatest favour during the last century as an explanation of simple jaundice, was the view that there was a spasmodic contraction of the bile ducts. This contraction became so great that it was impossible for the bile to pass down the ducts, no cavity being left, but merely a solid ligament.

* Bamberger, *Krankheiten des chylopoëtischen Systems*, in Virchow's *Handb. d. spec. Path. u. Ther.* Erlangen, 1864. 2te Aufl. p. 566.

After death, the spasm relaxed, and no traces of its existence could be found in the body. This idea of an *icterus spasmodicus* or *spasticus* would explain all those cases in which no palpable obstruction to the ducts was discovered, and could therefore be applied to those for which now-a-days the theory of a hæmatogenous jaundice, or the like, is brought in. The existence of a spasmodic jaundice was accepted by Peter Frank,* and many others; Cullen says: "such spasm may happen either in the duct itself, which we suppose to be contractile, or in the duodenum pressing the sides of the duct close together.†" The theory was used by Brüning to explain the appearance of *icterus epidemius*, and has continued down into our own time in vogue as a possible explanation of some kinds of jaundice.‡ It may be found even now spoken of here and there by certain French authors.§ Sir Thomas Watson says we can neither prove nor disprove it.||

* Peter Frank, *de cur. hom. morb. epitome*, Viennæ, 1821, Lib. vi. Pars iii. p. 320.

† Cullen, *First Lines of the Practice of Physic*, § MDCCCXVIII. Thomson's edition, Vol. ii. p. 656.

‡ Brüning, *de ictero spasmodico epidemico infantum Essendia*, Vesal. et Lips. 1773, quoted by Joseph Frank, *Prax. med. univ. præc.* Lips. 1843, Pars iii. Vol. ii. Sect. ii. t. i. p. 311.

§ Gubler, *Gaz. méd. de Paris*, 1854, p. 218.

|| Watson, *Lectures on the Principles and Practice of Physic*, Lond. 1857, 4th ed. Vol. ii. p. 609.

Howship has recorded a case in which he thinks he detected constriction of the ducts after death. A young man, aged 18, died after 48 hours of excruciating pain in the seat of the gall-bladder. After death the liver was found quite natural, the gall-bladder large, tense, and full. The large and small intestines contained a white mucous matter, but no trace of bile. The *ductus communis* being punctured with a lancet about its middle, a very small probe, with some difficulty, passed through it into the bowels. In the opposite direction it passed with tolerable ease by the hepatic duct into the liver. Howship found, dissecting still further, the impervious duct solid, contracted, tough, and opaque, like a soft ligamentous structure. After six hours and later the ducts had become perfectly relaxed. (*Practical Remarks on the Discrimination and Appearances of Surgical Disease*, London, 1840. p. 194.)

There is no mention of delirium; the skin was mottled as in scarlatina with an appearance of petechiæ; spots of blood in the stomach under the villous lining. It was not apparently a case of *icterus gravis*.

The hypothesis of *icterus spasmodicus* depends on the possible irritability of the bile ducts, and the hypothesis has therefore risen or fallen in favour according to the views taken of the presence of muscular fibres in the ducts leading from the liver.

It still seems to be an open question whether the ducts can be excited to contraction and whether they contain involuntary muscular fibres.

Magendie gave a great blow to the theory when he stated that he had never been able to see a trace of contraction in the gall ducts of mammals after any excitant.* It is denied by many† that the ducts contain any contractile elements; and those who do admit that muscular fibres are present, state that the development is very small and that it is not likely that they would be able to affect the bore of the duct.‡ Others maintain that the ducts are irritable, and contract on the application of various stimuli.§

Heidenhain was induced, from the irregularity with which the bile made its appearance in some of his biliary fistulæ, to enquire if the ducts really possessed contractile fibres. He thinks he has proved their existence. He placed the ducts, fresh from the animals, in a large volume of absolute alcohol for 24 hours; sections were laid for a few hours in chloride of palladium. (1:900) In a few hours, the sections were mounted in water or glycerine. The cylindrical epithelium could be seen well preserved. Under it was a well-marked layer of

* Magendie, *Précis élémentaire de Physiologie*, Paris, 1836, 4e éd. t. ii. p. 475.

† Henle, *Handb. d. system. Anat. des Menschen*, Braunschweig, 1866, Bd. ii. p. 217. Frey, *Handb. d. Histologie u. Histochemie*, Leipzig, 1867, p. 559. Cruveilhier, *Traité d'anatomie descriptive*, Paris, 1865-68, t. ii. p. 201.

‡ Kölliker, *Handb. d. Gewebelehre des Menschen*, Leipzig, 1867, 5te Auflage, p. 440. Leydig, *Lehrb. d. Histologie*, Frankfurt a. M. 1857. p. 356.

§ Longet, *Traité de Physiologie*, Paris, 1869, 3e éd. t. ii. p. 308. Colin, *Traité de Physiologie comp.* Paris, 1871, 2e éd. t. i. p. 785. Colin admits that the contraction is so feeble that no change in the diameter of the tube would be brought about. Henle (*loc. cit.*) was unsuccessful in his attempt to cause contraction of the ducts in a man recently beheaded.

a yellow colour, the elements of which ran, for the most part, in a circular direction, and in which numerous long nuclei were visible. Abundance also of longitudinal elements could be seen, not, however, clearly separated from the circular. The elements in the bundles of these circular fibres, might readily be taken for lymphoid cells, as there was often seen plainly a dark nucleus surrounded by brighter cell substance. With this marked layer was also a certain amount of connective tissue.

If it be true, as F. E. Schulze teaches, that only the contractile fibres are coloured yellow by palladium, then it follows that the thick well-marked layer, described by Heidenhain, is made up of these fibres.

Heidenhain also noted, in an experiment on a rabbit, that the flow of bile was much increased when the aorta was compressed. Now this may mean that the ducts of the liver contracted, as contractions of the bowels and uterus are also noted whenever the aorta is compressed.*

Audigé has reviewed the evidence of the contractility of the ducts, and like Heidenhain, has come to the conclusion: i. that there are muscular fibres in the bile ducts both of men and dogs; and ii. that the ducts of dogs show a notable contraction under the stimulus of electricity, or mechanical means. Audigé, nevertheless, will not admit of a spasmodic jaundice; but applies his view of spasm of the ducts to the cases in which a gall stone is coming down from the bladder.† Dujardin-Beaumetz has indorsed Audigé's observations.‡

It will be seen, therefore, that even those who assert the existence of muscular fibres in the ducts, and their

* Heidenhain, *Studien des phys. Inst. zu Breslau*, Leipzig, 1868. Heft iv. pp. 242-246.

† Audigé, *Recherches expérimentales sur le spasme des voies biliaires*, Paris, 1874.

‡ Dujardin-Beaumetz, *Bulletin de Thérapeutique*, 1873. t. lxxxv. p. 385.

contractile power, do not allow of the theory of *icterus spasmodicus*. Still, nervous influences upon the liver must not be lost sight of, so long as injury to the fourth ventricle of the brain, or to the sympathetic in the neck may work such results. It is true that it is the only instance known; but the influence of the nervous system upon the functions of the liver would probably form a rich field of research for the physiologist.* Vulpian believes that jaundice from emotion may be caused by a catarrh of the ducts, by an abundant polycholia, or by an inversion of the movement of the bile generated in the liver cells. He thinks it likely that the jaundice is catarrhal in the greater number.†

By the side of the spasmodic jaundice may be considered the paralytic jaundice, which was once thought to be due to a stagnation of the bile in the ducts, brought about by the gall ducts and gall bladder not having contracted to expel their contents.‡ This theory of jaundice was used by Th. von Dusch as an explanation of acute yellow atrophy, the cells of the liver being dissolved in the accumulated bile.§ Both these theories are now discredited.

Another explanation of the cause of simple jaundice, held in much favour at the present day, is that it is due to an extension of the catarrh of the duodenum and stomach to the common duct. The presence of symptoms of gastric disturbance undoubtedly lends much colour to this theory; and in my opinion it is in no way discredited by the criticisms of Sée, which are to the

* Heidenhain (or his pupils, *Arch. f. Anat. und Phys.* 1860. p. 667) is inclined to admit of an *icterus spasticus*, chiefly because the pressure under which the bile passes down the ducts is so small, and thus even a slight constriction would be enough to cause jaundice.

† Vulpian, *Cours sur la Bile*, 1874. Paris, recueilli par Paulier, p. 139.

‡ Erasmus Darwin, *Zoonomia*, Vol. ii. § xxx. Lond. 1801. Third ed. p. 3.

§ Th. v. Dusch, *Untersuchungen u. Experimente als Beitrag zur Pathogenes des Icterus*, Leipzig, 1854. p. 37.

effect that the stomach symptoms are not always those of gastric catarrh.* This is quite true; and there are some cases of simple jaundice in which there are no gastric symptoms whatever.

It is commonly said by the Germans that Stokes of Dublin was the first to teach the theory of *icterus catarrhalis*; but it certainly seems that van Swieten had some notion of the doctrine. He attributes the jaundice of the new-born to the thick meconium adhering to the walls of the duodenum; and says that even in grown-up people a mucous secretion remaining in the upper part of the intestine has been the cause of jaundice; and he gives the old quotation from Hippocrates to show that jaundice arising from phlegm is little dangerous and easily cured.†

It is sometimes said that Dr. John Hunter (not to be confounded with the great John Hunter, the Surgeon,) spoke of jaundice from catarrh or mucus in the ducts. He is speaking of the cause of the jaundice in remittent fever and says: "In the body of a person who died of pulmonary consumption, I had lately occasion to observe some things not altogether foreign to the present subject. A few days before death, to the common symptoms of the disease, was superadded a jaundice. The lungs were found diseased in the usual manner; there were adhesions to the pleura, tubercles, indurations, and suppurations in their substance. In the abdomen there were marks of superficial inflammation all over the liver, and the lower surface of it was united to the stomach by adhesions. The gall-bladder was full, but no bile could be squeezed out of it. On laying the *ductus communis* open from the *duodenum*, it was found filled with bile of a brown colour, and of a thick

* Sée, *Gaz. d. Hôp.* 1872. p. 201.

† G. van Swieten, *Comment.* § 950. Lugd. Bat. 1755. t. iii. p. 128. "Imo et in adultis pituitosa colluvies in primis viis hærens, icteri causa fuit."

and ropy consistence, as were also the *ductus hepatici*. Part of the *ductus cysticus* was laid open, and the gall-bladder was pressed with considerable force, but still no bile flowed. Through a blow-pipe introduced into the duct, the air at last with some difficulty was forced into the gall-bladder, after which by pressing again, a coagulum of bile was squeezed out, and what followed was ropy and black, like melasses. On laying the duct open all the way to the bladder, there appeared no other obstruction to the bile than the coagulum, which, as well as the thick and ropy state of that secretion, appear rather to have been the effects of stagnation than a cause of obstruction in the first instance. Did the inflammation in the neighbourhood of the ducts, and perhaps extending to them, excite such contractions in them as obstructed the bile, in the same way that a suppression of urine, is sometimes a consequence of inflammation, in the urinary passages?"*

Portal also says that a swelling of the duodenal glands from inflammation or any other cause, may bring about a jaundice by hindering the flow of bile into the duodenum.†

When Broussais taught that all diseases were more or less due to gastritis or duodenitis, it was necessary that diseases of the liver and ducts should follow the rest. Andral is one of the writers who have carried out this view. Several times, he says, he has found in the bodies of jaundiced persons no other change than a violent inflammation of the duodenum, which appeared to have extended to the bile ducts.‡

It was maintained by Stokes in his Lectures on Medicine, that the most important and most frequent

* John Hunter, M.D. *Observations on the Diseases of the Army in Jamaica*, London, 1796, See Ed. p. 158.

† Portal, *Observations sur la nature et le traitement des maladies du foie*, Paris, 1813, p. 154.

‡ Andral, *Clinique méd.* Paris, 1839, 4e éd. t. ii. p. 290.

cause of jaundice was disease of the mucous surface of the stomach and duodenum. It is not, however, due to any mechanical hindrance to the flow of bile, but to a "sympathetic irritation" of the liver, secondary to the gastritis. The biliary secretion is arrested. Stokes' theory is thus nothing more than the theory of jaundice by suppression, but the suppression is due to "sympathetic irritation" of the liver from the stomach.* Budd, on the other hand, really noticed a catarrhal plugging of the ducts: "It happens, however, not very unfrequently, that, on squeezing the hepatic ducts, a viscid whitish fluid oozes out, which, on examination through the microscope, is seen to be chiefly made up of the prismatic epithelial cells of the gall ducts."† Further: "many of the cases of simple jaundice coming on in healthy persons are probably cases of this kind." But later on he says: "In a large proportion, perhaps in the greater number of cases, jaundice results primarily and solely, from the secretion of bile being suppressed or deficient."‡ This explanation of simple jaundice as a jaundice by suppression was in great vogue twenty years ago, and even now traces of the doctrine may be met with, rather, however, in speech than in print.

But the writer who has done the most to advance catarrh of the bile ducts as a cause of simple jaundice to the favour in which it is now held by so many, is Virchow. This is another instance of a man, later on in life, destroying the work of his earlier days; for if the theory of hæmatogenous jaundice were received by any one, it was owing to the support which Virchow gave to it thirty years ago, on his entrance into life.§ But

* Stokes, *Lond. Med. and Surg. Journal*, 1834. vol. v. p. 198.

† Budd, *On Diseases of the Liver*, London, 1845. First edition, p. 150.

‡ Budd, *op. cit.* p. 383.

§ Virchow, *Gesamm. Abhandl.* Hamm, 1862, 2te Aufl. p. 849.

in 1865, Virchow declared himself in favour of the doctrine that jaundice arises always from the absorption of bile secreted beforehand, and showed from his experience that in many cases, unsuspected before, a catarrh of the ducts, or at least some obstruction to them, might be seen after death, if it were only carefully looked for.* This was at once taken up and applied afresh to the explanation of simple jaundice, and it certainly seems to me the best of all the theories which have yet been proposed. That a catarrh is a common cause of jaundice cannot I think be disputed, but that it is the cause of all cases of simple jaundice still lacks proof; a difficulty not likely to be overcome soon, as opportunity for examination after death is so rare.

Another explanation of simple jaundice has been set forth by Glax. The jaundice arises from changes in the circulation of the liver. These changes are due to the atony of the walls of the stomach and intestines, which so often show disorder in simple jaundice. If the tone of the walls of the stomach and intestine be decreased, the rapidity of the blood stream in the portal vein is decreased. This being the case, should any increase in the arterial pulsations appear, the ramifications of the hepatic artery, the portal vein, and the ducts in the liver will be pressed together; something must give way, and so the ducts which offer the least resistance suffer; the bile therefore passes into the central vein of the hepatic lobule.†

This theory would become more interesting if there were any evidence of the decrease of the rapidity of the stream in the portal vein. It would seem, however, probable, that if there be a catarrh of the stomach and

* Virchow, *Arch. f. path. Anat.* 1865, Bd. xxxii. p. 117.

† Glax, Virchow and Hirsch's *Jahresb. f.* 1875, Bd. ii. p. 235. Abstract from *Sitz.-Ber. des Vereins der Aerzte in Steiermark*, 1873-74.

intestines, there would be a greater flow of blood to them; and that the current in the portal vein would not be thereby decreased in rapidity. If, however, it can be shown that there is a decrease in the pressure of the blood in the vessels of the liver, I do not see any objection to the adoption of Frerichs' theory,* of which, however, Glax does not seem willing to avail himself.

Diagnosis. This is often a matter of some difficulty, and may be only cleared up by the recovery of the patient, when it becomes plain that the jaundice was simple.

Disease of other organs should be carefully excluded, especially of the heart and lungs. I have known the jaundice of nutmeg liver mistaken for a simple jaundice. Then the liver itself must be carefully examined, and if possible the state of the gall-bladder made out. Should this be found distended, and the liver not greatly enlarged, a certain advance is made in the diagnosis, and then if the patient be young and formerly in good health, and the gastric symptoms and freedom from pain well marked, the diagnosis may, with some likelihood, be made of simple jaundice.

The absence of pain is the great distinguishing feature in a diagnosis between simple jaundice and gall-stones. The liver in gall-stones is also much greater in size, the jaundice sets in after an attack of pain, and the staining of the skin and urine is much deeper. Simple jaundice shows little besides the staining of the tissues and the gastric symptoms.

Prognosis. If the diagnosis can be safely made, the prognosis becomes exceedingly good. But even in the mildest case, the mind of the practitioner cannot be quite easy; for it is these apparently typical cases of simple jaundice that now and then develope all the

* Frerichs, *op. cit.* Bd. i. p. 89.

symptoms of *icterus gravis*.* Until the grave symptoms come on there is no means whatever of distinguishing between ordinary simple jaundice and the jaundice which is the forerunner of *icterus gravis*. The line which separates these two must be very narrow. The same poison, such as a foul smell, which gives to one person a gastric or intestinal catarrh with jaundice, seems to lead in another to the same disorder, but with the addition of parenchymatous degenerations in all the glands and muscles, as well as of the stomach. It seems to be a question of degree, not of kind.

Treatment. It would be unwise to treat actively a disease which naturally ends in recovery. The treatment must therefore be limited to that which will certainly do no harm, and it will be profitable to keep the gastric symptoms only in view and to treat them. It is most important to avoid all means that may aggravate the state of the patient. For instance, a mercurial purge may be given at the onset of the disorder, if such be indicated by the sluggishness of the patient's bowels. But the repetition of this dose, or the daily administration of mercury, such as now and then may be heard of, is a serious damage to the patient. The same may be said of antimony, chloral, or any other drug which causes a parenchymatous degeneration of organs. For it will be impossible to tell how far from, or how near to, the border line that separates *icterus gravis* from simple jaundice the patient is, and the introduction of such a body as mercury into the œconomy may determine the arrival of the graver symptoms.

The best plan of treatment would seem to be to begin with a purgative, if the patient's bowels should not

* Icteri nunquam spernendi, nam sub larva ac persona icteri saepe magni, periculosi, ac repentini morbi absconduntur; et saepissime moriuntur derepente icterici, ut ait Dodonaeus. (Stoll, *Aphorism.* in *Rat. Med.* Viennæ, 1790, Pars vi. Sect. i. § 103. p. 29.)

be already too much open. The purgatives may be vegetable; the compound colocynth pill of the pharmacopœia; or to which a few grains of calomel may be added. Alkalies may then be administered, with bismuth, before food. The diet should be strictly regulated. All indigestible matters, as vegetables and fruit, must be forbidden; and the diet restricted to milk, soups, without vegetables, or in which vegetables have been boiled, and then strained out, and some small amount of farinaceous food. Coffee, tea, and alcohol must be forbidden. The patient may be allowed acid drinks, such as lemonade. As the gastric symptoms subside, white fish and then meat may be allowed, and the alkaline treatment may be changed to a course of *aqua regia*.

Emetics have long been a favourite remedy, and Sir Dominic Corrigan specially praises ipecacuan, by the action of which he thinks he has warded off the onset of the graver symptoms, and even cured a case of acute yellow atrophy.* I must own that ipecacuan, still more tartar emetic, appear to me dangerous remedies; for the diagnosis must be indeed certain before emetics can be given with confidence. They are supposed to act by compression of the gall-bladder and forcible expulsion of its contents into the duodenum. The serious results of violent efforts at vomiting, if a wrong diagnosis should chance to have been made, need scarcely be pointed out; if the ducts be obstructed by a gall-stone, or the head of the pancreas enlarged, vomiting seems more likely to be followed by a rupture of the bile passages behind the stone than by any good to the patient. Again, as Bamberger has quite correctly pointed out,† jaundice is not an unknown sequence of the administration of emetics themselves.

* Corrigan, *Dublin Hosp. Gaz.* 1845, pp. 69 and 71.

† Bamberger, *op. cit.* p. 568.

The same cautions must be applied to another method of treatment which Gerhardt has of late introduced, pressure and faradization of the gall-bladder. The employment of electricity is indeed not new, as Erasmus Darwin says that he gave half-a-score of smart electric shocks along the course of the bile ducts from a coated bottle to a man who had been jaundiced for six weeks, and the same day the stools became yellow.*

Gerhardt grasps the enlarged gall-bladder with his fingers, and endeavours to squeeze its contents out. He says that the gall-bladder may be felt gradually emptying itself, and a sort of fremitus appears to accompany it. After this, the gall-bladder can no longer be made out by percussion, and on the second day the fæces become coloured. Gerhardt also places one electrode over the gall-bladder, the other on the spine at a level with the first, and then passes strong induction currents between the two; after three or four days the stools become coloured.†

For my own part I should scarcely like to adopt such active measures. It would be altogether different if the advantage to the patient were to be great, as the taxis in hernia; but the disease here is a very mild one, and the remedy may possibly prove worse than the disease. I do not think that it is justifiable to expose the patient to the risk of rupturing the ducts or the gall-bladder; and if the theory of jaundice from catarrh of the stomach and duodenum be allowed, the primary disease would not be overcome by the ejection of the plug of mucus into the duodenum, but it is probable that the plug would be renewed, the catarrh remaining, as soon as the excess of bile had passed through the papilla. In-

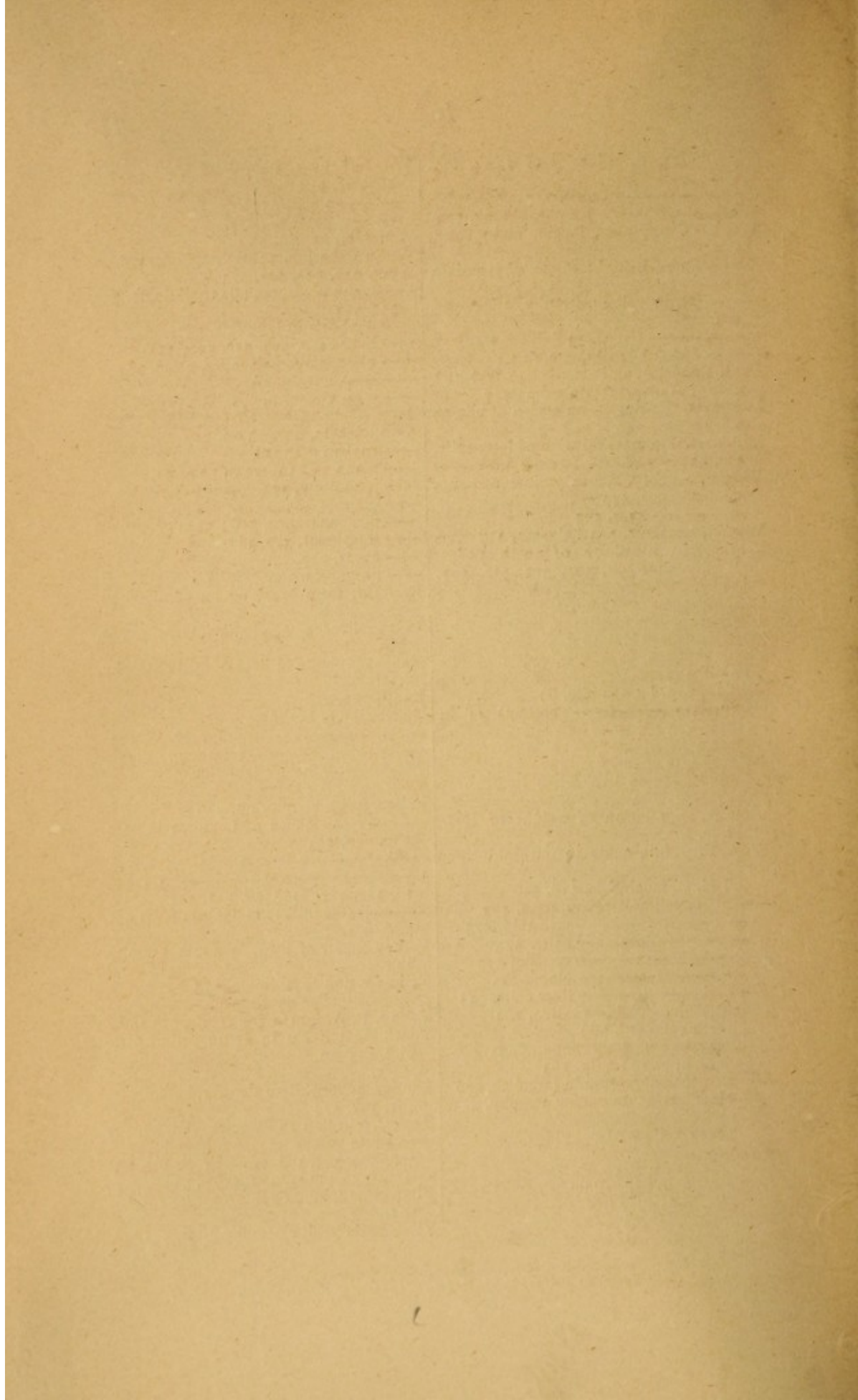
* Erasmus Darwin, *Zoonomia*, § xxx. Lond. 1801. 3rd Ed. Vol. ii. p. 2.

† Gerhardt, *Ueber Icterus gastro-duodenalis*, in Volkmann's *Sammlung klin. Vorträge (Innere Medicin.)* Leipzig, 1870-75, p. 112.

deed, the passage of the bile over the mucous membrane is not likely to aid its recovery.

Krull recommends the daily injection of cold water into the rectum. He says it has been so successful that he has never had to repeat it more than seven times. One or two litres (from two to four pints) of a temperature of 60° F. (15° C.) are thrown up the bowel, and allowed to be retained as long as possible. The temperature of the water must be gradually raised with each successive injection.*

* Krull, *Berlin. klin. Woch.* 1877, p. 159.



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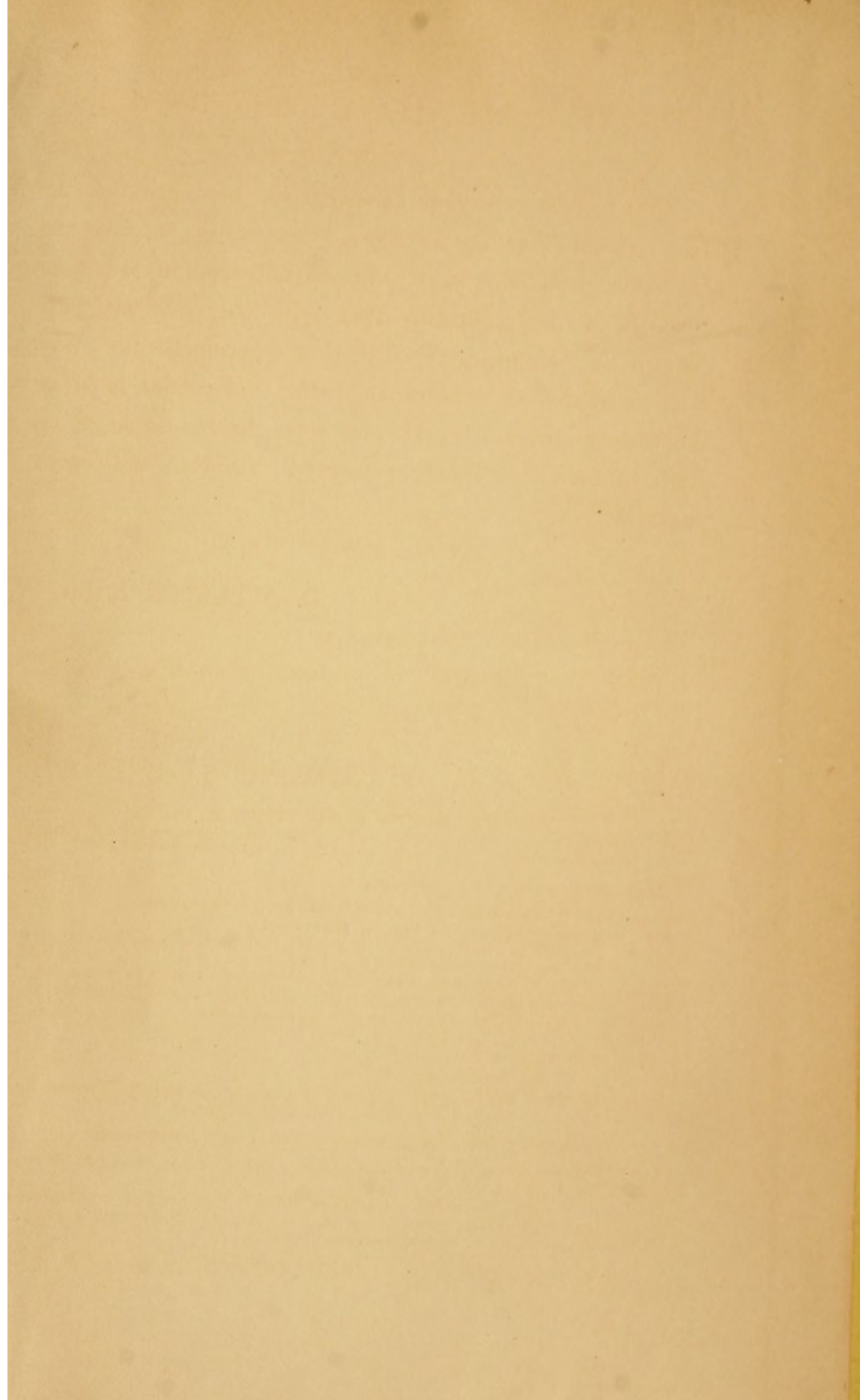
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