is necessary to intestinal digestion, that it contains excrementitious matters and that the cells constantly produce glycogen. The liver produces urea, which is excreted, however, chiefly by the kidneys. It may also effect certain changes in digested and foreign matters that are absorbed from the alimentary canal. As regards its varied uses, therefore, as well as in its anatomy, it has no analogue in the glandular system, and the mechanism of its action is necessarily complex.

As regards the secretion of bile, the only view that is consistent with actual knowledge is that this fluid is produced by the liver-cells and is taken up by the plexus of bile-ducts which surrounds these cells. The little glandular organs that are attached to the larger branches of the duct secrete mucus which gives the viscidity observed in the bile of some animals. The bile, indeed, is viscid in different animals in proportion to the development of these mucous glands; and in the rabbit, in which the glands do not exist, the bile has no viscidity (Sappey). The passage of excrementitious substances from the blood into the bile will be discussed in connection with the action of the liver as an organ of excretion, and the formation of glycogen will be considered in its proper place.

Of course the circulation of blood in the liver is a condition necessary to the secretion of bile. As regards the question of the production of bile from venous or arterial blood, it has been shown that the materials out of which the bile is formed may be supplied by either the hepatic artery or the portal vein. Bile is secreted after the hepatic artery has been tied, and also after the portal vein has been gradually obliterated, the hepatic artery being intact (Oré). Bile is produced in the liver from the blood distributed in its substance by the portal vein and the hepatic artery, and not from the blood of either of these vessels exclusively; and bile may continue to be secreted, if either one of these vessels be obliterated, provided the supply of blood be sufficient.

Some of the variations in the discharge of bile have been described in connection with the physiology of digestion; but although the bile is poured out much more abundantly during intestinal digestion than at other times, its production and discharge are constant. The bile is stored up in the gall-bladder to a considerable extent during the intervals of digestion. If an animal be killed at this time, the gall-bladder is always distended; but it is found empty, or nearly so, in animals killed during digestion.

The influence of the nervous system on the secretion of bile has been very little studied, and the question is one of great difficulty and obscurity. The liver is supplied very abundantly with nerves, both cerebro-spinal and sympathetic, and some observations have been made upon the influence of the nerves upon its glycogenic action; but with regard to the secretion of bile, there is little to be said beyond what has already been stated concerning the influence of the nervous system on other secretions.

The bile is discharged through the hepatic ducts like the secretion of any other gland. During digestion the fluid accumulated in the gall-bladder passes into the ductus communis, in part by contractions of its walls, and in part, probably, by compression exerted by the distended and congested digestive organs adjacent to it. It seems that this fluid, which is necessarily produced by the liver without intermission, separating from the blood certain excrementitious matters, is retained in the gall-bladder for use during digestion.

Quantity of Bile.—The estimates of the daily quantity of bile in the human subject must be merely approximate; and the ideas of physiologists on this point are derived chiefly from experiments upon the inferior animals. The most complete and reliable observations upon this subject are those of Bidder and Schmidt, which were made upon animals with a fistula into the gall-bladder, the ductus communis having been tied. These observers found great variations in the daily quantity in different classes of animals, the quantity in the carnivora being the smallest. Applying their results to the human subject, assuming that the amount is about equal to the quantity secreted by the carnivora, the daily secretion in a man weighing one hundred and forty pounds (63·5 kilos.) would be about two and a half pounds (1,134 grammes).

Uses of the Bile.

The uses of the bile in digestion have already been fully described; but before considering its characters as an excretion, it will be necessary to study its general properties and composition.

Properties and Composition of the Bile.—The secretion as it comes directly from the liver is somewhat viscid; but after it has passed into the gall-bladder, its viscidity is much increased by a farther admixture of mucus.

The color of the bile is very variable within the limits of health. It may be of any shade between a dark, yellowish-green and a reddish-brown. It is semi-transparent, except when the color is very dark. In different classes of animals the variations in color are very great. In the pig it is bright-yellow; in the dog it is dark-brown; and in the ox it is greenish-yellow. As a rule the bile is dark-green in the carnivora and greenish-yellow in the herbivora.

The specific gravity of the human bile is 1020 to 1026. When the bile is perfectly fresh it is almost inodorous, but it readily undergoes putrefactive changes. It has a disagreeable and bitter taste. It is not coagulated by heat. When mixed with water and shaken, it becomes frothy, probably on account of the tenacious mucus and its saponaceous constituents.

It is generally stated that the bile is alkaline. This is true of the fluid discharged from the hepatic duct, although the alkalinity is not strongly marked; but the reaction varies after it has passed into the gall-bladder. Bernard found it sometimes acid and sometimes alkaline in the gall-bladder, in animals (dogs and rabbits) killed under various conditions; but many of these animals were suffering from the effects of severe operations. In the hepatic ducts the reaction is always alkaline; and there are no observations on human bile that show that the fluid is not alkaline in all of the biliary passages.

The epithelium of the biliary passages is strongly tinged with yellow, even in living animals. This is due to the facility with which the coloring matter of the bile stains the animal tissues. This is very well illustrated in icterus, when even a small quantity of this coloring matter finds its way into the circulation.

Perfectly normal and fresh bile, examined with the microscope, presents a certain quantity of mucus, the characters of which have already been described. There are no formed anatomical elements characteristic of this fluid. The fatty and coloring matters are in solution and not in the form of globules or granules.

COMPOSITION OF HUMAN BILE. (ROBIN.)

Water	916·00	to	819·00
Sodium taurocholate	56·50	"	106·00
Sodium glycocholate	traces.		
Cholesterine	0·62	to	2·66
Bilirubin	14·00	"	30·00
Lecithene; Palmitine, oleine and traces of soaps	3·20	"	31·00
Choline	traces.		
Sodium chloride	2·77	to	3·50
Sodium phosphate	1·60	"	2·50
Potassium phosphate	0·75	"	1·50
Calcium phosphate	0·50	"	1·35
Magnesium phosphate	0·45	"	0·80
Salts of iron	0·15	"	0·30
Salts of manganese	traces	"	0·12
Silicic acid	0·03	"	0·06
Mucine	traces.		
Loss	3·43	to	1·21
	1,000·00		1,000·00

There are no peculiarities in the composition of the bile, in respect to its inorganic constituents, which demand more than a passing mention. It contains no coagulable organic matters except mucine, and all of its constituents are simply solids in solution. The quantity of solid matter is very large, and the proportion of water is relatively small. Among the inorganic salts, sodium chloride exists in considerable quantity, with a large proportion of phosphates. There exist, also, salts of iron and of manganese, with a small quantity of silicic acid.

The fatty and saponaceous constituents demand hardly any more extended consideration. A small quantity of palmitine and oleine are held in solution, partly by the soaps, but chiefly by the sodium taurocholate. The fats sometimes exist in larger quantity, when they may be discovered in the form of globules. The proportion of soaps is very small. Lecithene ($C_{44}H_{90}NPO_9$) is a neutral, fatty substance extracted from the bile, and may be decomposed into phosphoric acid and glycerine. Choline ($C_5H_{15}NO_2$) is an alkaloid found in the bile in exceedingly minute quantity.

Biliary Salts.—In human bile the characteristic biliary salt is a combination of taurocholic acid ($C_{26}H_{45}NSO_7$) with sodium. A very small quantity of sodium exists in combination with glycocholic acid ($C_{26}H_{43}NO_6$). These

two salts were discovered in the bile of the ox, by Strecker, in 1848. Sodium glycocholate exists in quantity in ox-gall. Both of these salts may be precipitated from an alcoholic extract of bile by an excess of ether. The taurocholate is precipitated in the form of dark, resinous drops which crystallize with difficulty. The glycocholate is readily crystallizable. The biliary salts are very soluble in water and in alcohol. Their reaction is neutral.

There can be no doubt that the biliary salts are products of secretion and are formed in the substance of the liver. In no instance have they ever been discovered in the blood in health; and although they present certain points of resemblance with some of the constituents of the urine, they have never been found in the excreta. In experiments made by Müller, Kunde, Lehmann and Moleschott, on frogs, in which the liver was removed and the animal survived several days—and in the observations of Moleschott, between two and three weeks—it was found impossible to determine the presence of the biliary salts in the blood. There is no reason, therefore, for supposing that these salts are products of disassimilation. Once discharged into the intestine, they undergo certain changes and can no longer be recognized by the usual tests; but experiments have shown that, changed or unchanged, they are absorbed with the products of digestion. They are probably concerned in the digestive action of the bile.

Cholesterine.—Cholesterine ($C_{26}H_{44}O$) is a normal constituent of various of the tissues and fluids of the body. Most authors state that it is found in the bile, blood, liver, nervous tissue, crystalline lens, meconium and fæcal matter. It is to be found in all these situations, with the exception of the fæces, where it does not exist normally, being transformed into stercorine in its passage down the intestinal canal.

In the fluids of the body cholesterine exists in solution; but by virtue of what constituents it is held in this condition, is a question that is not entirely settled. It is stated that the biliary salts have the power of holding cholesterine in solution in the bile, and that the small quantity of fatty acids contained in the blood holds it in solution in that fluid; but direct experiments on this point are wanting. In the nervous tissue and in the crystalline lens, it is united with the other substances which go to make up these parts. After it is discharged into the intestinal canal, when it is not changed into stercorine it is to be found in a crystalline form, as in the meconium, and in the fæces of certain animals in a state of hibernation. In pathological fluids and in tumors, it is found in a crystalline form and may be detected by microscopical examination.

Cholesterine is usually described as an alcohol, having many of the properties of the fats, but not that of saponification with the alkalies. It is neutral, inodorous, crystallizable, insoluble in water, soluble in ether and very soluble in hot alcohol, though sparingly soluble in cold alcohol. It is inflammable and burns with a bright flame. It is not attacked by the alkalies even after prolonged boiling. When treated with strong sulphuric acid it strikes a peculiar red color.

Cholesterine may easily and certainly be recognized under the microscope by the form of its crystals. They are rectangular or rhomboidal, very thin and transparent, of variable size, with distinct and generally regular borders, and frequently arranged in layers, with the borders of the lower strata showing through those which are superimposed. The plates of cholesterine are often marked by a cleavage at one corner, the lines running parallel to the borders. Frequently the plates are rectangular, and sometimes they are almost lozenge-shaped. Crystals of cholesterine melt at 293° Fahr. (145° C.), but they are formed again when the temperature falls below that point.

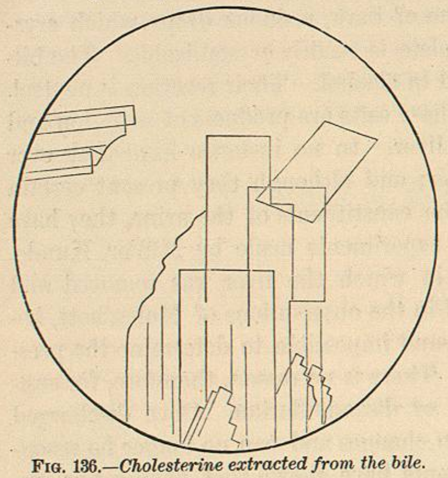

FIG. 136.—*Cholesterine extracted from the bile.*

The proportion of cholesterine in the bile is not very large. In the table, it is estimated at 0·62 to 2·66 parts per thousand. In a single examination of the human bile, the proportion was 0·618 of a part per thousand (Flint).

The origin and destination of cholesterine involve an office of the liver which has not been generally recognized by physiologists; and these questions will be considered specially, under the head of the excretory action of the liver.

Bilirubin.—The coloring matter of the bile, bilirubin ($C_{32}H_{36}N_4O_6$), bears a certain resemblance to the coloring matter of the blood and is supposed to be formed from it in the liver. It gives to the bile its peculiar tint and has the property of coloring the tissues with which it comes in contact. Whenever the flow of bile is obstructed for any considerable time, the coloring matter is absorbed by the blood and can be readily detected in the serum and in the urine. It also colors the skin and the conjunctiva. It is soluble in chloroform, by which it is distinguished from biliverdine, and forms soluble combinations with alkalies, in which form it is thought to exist in the bile. It probably is formed in the liver from the hæmoglobine of the red blood-corpuscles. When exposed to the air or to the influence of certain oxidizing agents, it assumes a greenish color and is changed into biliverdine. It is unnecessary to follow the various other changes produced by spontaneous decomposition or by the action of reagents.

Tests for Bile.—A simple test for bile-pigment is the following: A thin stratum of the liquid to be tested is placed upon a white surface, as a porcelain plate, and to this is added a drop of nitroso-nitric acid. If the coloring matter of the bile be present, a play of colors will be observed surrounding the drop of acid. The color will rapidly change from green to blue, red, orange, purple and finally to yellow. This test is applicable only to the coloring matter and does not detect the biliary salts.

A very delicate test for the biliary salts in a clear solution not containing albumen is what is known as Pettenkofer's test: To the suspected liquid are added a few drops of a strong solution of cane-sugar. Sulphuric acid is then slowly added, to the extent of about two-thirds of the bulk of the liquid. It is recommended to add the acid slowly, so that the temperature shall be but little raised. If a large quantity of the biliary salts be present, a red color shows itself almost immediately at the bottom of the test-tube, and this soon extends through the entire liquid, rapidly deepening until it becomes dark lake or purple. If the biliary matters exist in very small proportion, it may be several minutes before a red color makes its appearance, and the change to a purple is correspondingly slow, the whole process occupying fifteen to twenty minutes.

Excretory Action of the Liver.

Although the liver produces a greater or less quantity of urea, this substance is discharged from the body chiefly in the urine and mere traces exist in the bile. The excretory action of the liver will be considered, in this connection, with reference to the bile itself. At the present day it is generally admitted that the bile is an excretion as well as a secretion; and this question has been fully discussed in connection with the physiology of digestion. The confusion that has arisen with regard to this point has been due to the fact that those who adopted the view that the bile was simply an excretion denied to it any digestive properties; while on the other hand, those who believed it to be concerned in digestion would not admit that it was an excretion. It will be useful, as bearing upon the probable office of the bile as an excretion, to apply to this fluid the general law of the distinctions between secretions and excretions.

Cells of glandular epithelium are constantly forming, out of materials furnished by the blood, the characteristic constituents of the true secretions; but these do not pre-exist in the blood, they appear first in the secreting organ, and they never accumulate in the system when the action of the secreting organ is disturbed. Again, the true secretions are not discharged from the body, but they have an office to perform in the economy, and are poured out by the glands intermittently, at the times when this office is called into action. As far as the biliary salts, sodium taurocholate and sodium glycocholate, are concerned, the bile corresponds entirely to the true secretions. These salts are formed in the liver, they do not pre-exist in the blood, and they do not accumulate in the blood when their formation in the liver is disturbed. The researches of Bidder and Schmidt and others have shown that although the biliary salts can not be detected in the blood or chyle coming from the intestine, they are not discharged in the fæces. These facts point to an important office of the bile as a secretion. It is true that the bile is discharged constantly, but during digestion its flow is very much more abundant than at any other time. It is pretty well established that during the intervals of the flow of the secretions, the glands are forming the materials of secretion, which are washed out, as it were, in the great afflux of blood which takes place during what has been called the activity of the gland.

The constant and invariable presence of cholesterine in the bile assimilates it in every regard to the excretions, of which the urine may be taken as the type. Cholesterine always exists in the blood and in certain of the tissues of the body. It is not produced in the substance of the liver, but is merely separated from the blood by this organ. It is constantly passed into the intestine, and is discharged, although in a modified form, in the fæces. Physiologists know of no office which it has to perform in the economy, any more than urea or any other of the excrementitious constituents of the urine. It accumulates in the blood in certain cases of organic disease of the liver and gives rise to symptoms of blood-poisoning.

Origin of Cholesterine.—Cholesterine exists in largest quantity in the substance of the brain and nerves. It is also found in the substance of the liver—probably in the bile contained in this organ—the crystalline lens and the spleen; but with these exceptions, it is found only in the nervous tissue and blood. It is either deposited in the nervous matter from the blood or it is formed in the brain and taken up by the blood. This is a question, however, which can be settled experimentally.

In a series of experiments made in 1862, it was invariably found that the proportion of cholesterine in the blood of the internal jugular vein and the femoral vein was greater than in the arterial blood. In experiments made on dogs not etherized, the blood of the jugular vein contained, in one instance 23·3 and in another 59·8 per cent. more cholesterine than the arterial blood of the same animals. The blood of the femoral vein contained about 6·3 per cent. more cholesterine than arterial blood. In three cases of hemiplegia, cholesterine was found in normal quantity in blood taken from the arm of the sound side, while blood from the paralyzed side contained no cholesterine (Flint).

These observations point to the production of cholesterine in the tissues; and the fact of its existence, under normal conditions, in the nervous tissue renders it probable that the chief seat of its production is the substance of the nerve-centres and nerves. The question of its formation in the spleen is one that has not been investigated.

In another series of experiments, it was shown that the blood lost cholesterine in passing through the liver. In one observation it was found that the arterial blood lost a little more than 23 per cent. and the portal blood, about $4\frac{1}{2}$ per cent., in passing through the liver (Flint).

The portal blood, as it goes into the liver, contains but a small percentage of cholesterine over the blood of the hepatic vein, while the percentage in the arterial blood is large. The arterial blood is the mixed blood of the entire system; and as it probably passes through no organ which diminishes its cholesterine before it goes to the liver, it contains a quantity of this substance which must be removed. The portal blood, coming from a limited part of the system, contains less cholesterine, although it gives up a certain quantity. In the circulation in the liver, the portal system largely predominates and is necessary to other important actions of this organ, such as the production of glycogen; but soon after the portal vein enters the liver, its blood becomes mixed with that from the hepatic artery, and from this mixture the cholesterine is separated. It is necessary only that blood, containing a certain quantity of cholesterine, should come in contact with the bile-secreting cells, in order that this substance shall be separated. The fact that it is eliminated by the liver is proved with much less difficulty than that it is formed in the nervous system. In fact, its presence in the bile, and the necessity of its constant removal from the blood, consequent on its constant formation and absorption by this fluid, are almost sufficient in themselves to warrant the conclusion that it is eliminated by the liver.

In treating of the composition of the fæces, the changes which the cholesterine of the bile undergoes in its passages down the intestinal canal have been so fully considered that it is not necessary to refer to this portion of the subject again. But one examination only was made of the quantity of stercorine contained in the daily fæcal evacuation; and assuming that the quantity of cholesterine excreted by the liver is equal to the stercorine found in the evacuations, the quantity in twenty-four hours is about ten and a half grains (0·68 gramme). This corresponds with the estimates of the daily quantity of cholesterine excreted, calculated from its proportion in the bile and the estimated daily quantity of bile produced by the liver.

To complete the chain of the evidence leading to the conclusion that cholesterine is an excrementitious product which is formed in certain of the tissues and eliminated by the liver, it is necessary only to show that it may accumulate in the blood when the eliminating action of the liver is interrupted.

In a case of simple jaundice from duodenitis, in which there was no great disturbance of the system, a specimen of blood taken from the arm presented undoubted evidences of the coloring matter of the bile, but the proportion of cholesterine was not increased, being only 0·508 of a part per thousand. The fæces contained a large proportion of saponfiable fat, but no cholesterine or stercorine.

In a case of cirrhosis with jaundice, there was ascites, with great general prostration. This patient died a few days after the blood and fæces had been examined, and the liver was found in a condition of cirrhosis, with the liver-cells shrunken and the gall-bladder contracted. In this case the blood contained 1·85 of a part of cholesterine per thousand, more than double the largest quantity found in health. The fæces contained a small quantity of stercorine.

Inasmuch as cases frequently present themselves in which there are evidences of cirrhosis of the liver with little if any constitutional disturbance, while others are attended with grave nervous symptoms, it seemed an interesting question to determine whether it be possible for cholesterine to accumulate in the blood without the ordinary evidence of jaundice. An opportunity occurred of examining the blood in two strongly contrasted cases of cirrhosis, in neither of which was there jaundice. One of these patients had been tapped repeatedly—about thirty times—but the ascites was the only troublesome symptom and the general health was little impaired. In this case the proportion of cholesterine in the blood was only 0·246 of a part per thousand, considerably below the quantity ordinarily found in health. The other patient had cirrhosis, but he was confined to the bed and was very feeble. The proportion of cholesterine in the blood in this case was 0·922 of a part per thousand, a little above the largest proportion found in health. A few other pathological observations of this kind are on record. Picot, in 1872, reported a fatal case of "grave jaundice," in which he determined a great increase in the quantity of cholesterine in the blood, the proportion being 1·804 per 1000.

It is probable that organic disease of the liver, accompanied with grave symptoms generally affecting the nervous system, does not differ in its pathology from cases of simple jaundice in the fact of retention of the biliary salts in the blood; but these grave symptoms, it is more than probable, are due to a deficiency in the elimination of cholesterine and its consequent accumulation in the system. Like the accumulation of urea in structural disease of the kidney, this produces blood-poisoning; and this condition may be characterized by the name Cholesteræmia, a term expressing a pathological condition, but at the same time indicating the physiological relations of cholesterine.

Koloman Müller, in 1873, succeeded in injecting cholesterine into the blood-vessels without producing any effects due to mechanical obstruction of the circulation. He made a preparation by rubbing cholesterine with glycerine and mixing the mass with soap and water. He injected into the veins of dogs, 2·16 fluidounces (about 64 c. c.) of this solution, containing about 69 grains (4·5 grammes) of cholesterine. In five experiments of this kind, he produced a complete representation of the phenomena of "grave jaundice."

In view of all these facts, an excretory action of the liver, involving the separation of cholesterine from the blood and its discharge in the fæces in the form of stercorine, must be regarded as established, as well as the existence of cholesteræmia as a definite pathological condition.

Formation of Glycogen in the Liver.

In addition to the uses of the liver already described, this organ constantly produces in health a substance resembling starch, called glycogen, which is converted into glucose and is carried into the circulation by the hepatic veins. In this way the liver acts as a ductless gland, glycogen being formed by the liver-cells in precisely the manner that the various constituents of the secretions are produced by other glands. The discovery of this, which was first called the sugar-producing office of the liver, was made by Bernard, in 1848. During the present century there have been few discoveries which have attracted so much attention, and Bernard's experiments have been repeated and extended by physiologists in different parts of the world. In 1857, Bernard discovered glycogen in the liver and showed that the production of this substance precedes the formation of sugar. In studying, then, the mechanism of sugar-production in animals, it will be necessary to begin with the physiological history of glycogen.

Glycogen ($C_6H_{10}O_5$) belongs to the class of carbohydrates and is isomeric with starch. It is readily converted into glucose ($C_6H_{12}O_6$). In nearly all regards it has the properties of starch, but it gives a deep red color with iodine instead of a blue. In the liver-cells it exists in the form of amorphous granules surrounding the nuclei. It may be extracted from a decoction of the liver-substance, by precipitating the albuminoids by adding alternately dilute hydrochloric acid and potassio-mercuric iodide, filtering and treating the filtrate with an excess of alcohol. The alcoholic precipitate, washed with alcohol and dried rapidly, is in the form of a white powder, which will keep indefinitely. In the adult, glycogen is most abundant in the liver; but it has been found in small quantity in the muscular substance, in cartilage and in certain cells in process of development. In the early months of fœtal life it exists in nearly all the tissues. It is found, also, in cells attached to the villi of the placenta.

The most important of the conditions which influence the quantity of glycogen in the liver relate to alimentation and digestion. The liver always contains more glycogen during digestion than in fasting animals. After a few days of starvation, glycogen may almost or quite disappear from the liver. This also occurs in animals fed for a time exclusively with fats, and the quantity is diminished by a purely albuminous diet as contrasted with a mixed diet. Still, as was shown by Bernard, glycogen is invariably present in the livers of healthy carnivorous animals that have always been fed with meat alone.

A very great increase in the quantity of glycogen in the liver is produced by feeding animals largely with carbohydrates. Not only are the starches apparently stored up for a time in the form of glycogen in the liver, but sugars seem to undergo a change into glycogen which accumulates in the liver. This is to be expected, as the starches are changed into sugar before they are absorbed, and all the carbohydrates behave in the same way as regards general nutrition. Very abundant alimentation with carbohydrates sometimes produces a temporary diabetes, the quantity of sugar in the blood increasing to such an extent that sugar is discharged in the urine. This is due either to the passage of a certain quantity of sugar unchanged through the liver or to an excessive formation of glycogen, which is more actively changed into sugar than under normal conditions.

As far as regards the influence of alimentation upon the formation of glycogen, it seems probable that in the herbivora and in man the chief source of hepatic glycogen is the class of alimentary substances called carbohydrates; but the fact that glycogen exists in the livers of the carnivora, and probably in man, under a nitrogenized diet, shows that the liver is capable of forming glycogen from the albuminoids.

Change of Glycogen into Sugar.—It is almost certain that the liver does not contain sugar during life. Many years ago (1858) this fact was recognized by Pavy, and it has since been confirmed by other physiologists. Pavy, however, assumed that there was no such thing as sugar-formation by the liver, under absolutely normal conditions. He regarded the sugar found in