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THE CONCEPT OF ASSIMILATORY SYSTEM OF PAULESCU DATING FROM 1912

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INTRODUCTION

It is worthy to note that the final paper consider to be "birth certificate" of insulin has been published by Paulescu on 31 august 1921 in "Archives Internationales de Physiologie et Biochimie" entitled *"**Recherche sur le role du pancreas dans l'assimilation nutritive**"*. The root of this great discovery can be found earlier in the 3th volume of the famous "***Traite du Medicine Lancereaux-Paulesco***" published in 1912 in Paris (J.B. Bailliere & Fils).

In the physiological view of Paulescu, the liver is an organ working together with the pancreas in order to accomplish *"**the assimilatory function**"*. In the Chapter VII entitled "The Liver" we found the following statement: "the liver has to blood circulations: a nutritive one, representative by the hepatic artery, and a functional one, represented by the portal vein.

In the "Physiology" subchapter he mentioned as one of the main function that to transform some of absorbed proteins, lipids and carbohydrates in order to render them assimilable by the various peripheral tissues. Here, he mentioned the capacity of this organ to store glucose as glycogen and for that *"the liver can be assisted by the internal secretion of the pancreas. This intervention is less visible when glycogen is stored in the muscular fibres"*.

These data clearly show that for Paulescu, the main function of the internal secretion of the pancreas is that to make the proteins, lipids and carbohydrates assimilable in the various peripheral tissues.

Apart this observations it is worthy to note that Romanian hepatology have in this chapter of this famous old treat of medicine, a very strong and valuable root.

TRAITÉ DE MEDÉCINE LANCEREAUX–PAULESCO

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VII – THE LIVER

SECTION I
MORPHOLOGY AND PHYSIOLOGY

The liver, the largest organ in the body, is a gland deriving from the intestine from which it differs through the modifications it produces on food substances that it stores temporarily, with the aim of turning them into nurturing material for the tissues, namely for assimilation. This is its main function, which is completed by the secretion of the bile.

It is also attributed the capacity to neutralize certain toxic substances absorbed by the intestine.

Embryology – The liver lies in the ventral side of the duodenum, as a tubular invagination which divides and subdivides itself so as to form the bile ducts. The last branches of these byways suffer an anastomosis and form the liver excreting tubes. This glandular product is surrounded by the embryonic conjunctive tissue; it develops around the umbilical vein. This vein has branches which interconnect, combine with the glandular tubes and form the liver blood system.

As it grows, the organ occupies the space between the two foils of the ventral mesenteric muscle, which will turn into the peritoneal cover and the ligaments (suspensor ligament, epiploon,

gastro-hepatic). It quickly reaches a considerable volume and, towards the third month of embryonic life, it fills up almost the entire abdominal cavity. Around the same period, it starts secreting the bile, which accumulates in the intestine forming the meconium.

After birth, following circulation suppression in the umbilical vein[1] – the liver volume increases more slowly than that of other organs in the body.

Anatomy – The liver lies in the right upper side of the abdominal cavity, right under the diaphragm, whose breathing and pathologic movements it follows. It is fixed in this position by the related blood vessels, which penetrate the lower vena cava and by the peritoneal folds which attach it to the diaphragm and the abdominal walls.

In adults, the liver weighs around 1500 g; its length averages 25 cm transversally, 20 cm on the anterior-posterior axis and its usual width is 7 cm. However, its dimensions have large individual and especially pathologic variations.

Reddish-brown in color, with a granitic aspect, the liver has a smooth surface and a relatively firm and elastic consistency; however, it is easily friable and, once the capsule is uncovered, it can be easily crushed.

It is made of two unequal lobes (the left is smaller than the right) and has a convex and united superior face, onto which the suspensor ligament is attached, whose insertion line marks the distinction between the two hepatic lobes. This face unites with the diaphragm which separates it from the heart and the lungs; to the front, it exceeds the costal arch and comes in immediate contact with the abdominal wall.

The anterior superior surface is limited by the anterior liver margin, which is thin and clear and, when projected onto the anterior abdominal wall, creates an oblique line which originates to the right under the false ribs, exceeding by one or two finger widths the 9^{th} and 8^{th} ribs, crosses the epigastrium and disperses under the anterior margin of the 7^{th} left rib. In relation with the abdominal wall, the position of this margin provides individual variations, more visible in pathological conditions. It has two indentations, one in the suspensor ligament insertion and the other to the right of the previous one, at bile level.

The inferior liver surface, highly irregular, has to the left an anteroposterior channel connected to the insertion line of the suspensor ligament on the superior surface, which separates the two hepatic lobes. This channel hosts the fibrous cord replacing the umbilical vein in the anterior half and the cord replacing the Aratius duct in the posterior half.

Another channel, parallel with the previous one, located about 7 cm to its right, hosts the gallbladder in the anterior half and the inferior vena cava in the posterior half.

A third transversal channel unites the two previously-mentioned ones; it forms the *liver hilum* which is the access doorway for blood vessels, nerves and the places which allow the exit of bile and lymphatic ducts, organs contained in the gastro-hepatic epiploon.

These three channels create four segments on the inferior liver surface:

1. the segment located to the left of the umbilical vein channel represents the inferior surface of the liver and enters into contact with the antero superior surface of the stomach;

2. the segment located to the right of the bile duct connects to the front and the back with the colon, kidney and suprarenal glands;

3. the segment contained between these two channels located in front of the transversal channel represents the square hepatic lobe and is attached to the duodenum;

4. the lobe of Spiegel, located behind the transversal channel, is connected with the inferior cavity of the epiploons, the heart, the celiac trunk, the solar plexus and the upper pancreatic margin.

The posterior liver edge corresponds with the diaphragm and the organs going from the thorax to the abdomen (esophagus, aorta, inferior vena cava).

The right liver edge occupies the right hypochondrium; it's left edge advances into the left hypochondrium, between the diaphragm and the stomach, but does not reaches contact with the gallbladder, at least not in adults.

This shape of the liver is sometimes altered by lesions such as syphilis gumma, obliteration of the portal vein branches, hydatid cysts etc., which, by destroying certain parts of the parenchyma, causes the hypertrophy of the remaining gland and the increase in volume of its histologic elements.

[1] The umbilical vein, which brings the blood carried by placenta arteries to the inferior vena cava, crosses the navel, follows the lower edge of the liver suspensor ligament, reaches the longitudinal channel of the inferior liver face and reaches the bile. There it divides into two branches, out of which one unites with the left branch of the portal vein, and the other moves forward and reaches the inferior vena cava, forming the Arantius venous duct. Afterbirth, these veins, which are devoid of blood, obliterate and turn into fibrous cords.

Histology – The liver is covered by the peritoneum, which is located, as are the other abdominal organs, outside the cavity of the serous membrane.

In order to understand the location of the hepatic peritoneum, we have to consider the gland in its normal condition, with the fibrous cord (umbilical vein) uniting it to the navel, with the blood vessels and the excreting ducts entering or leaving the hilum. Under these conditions, the peritoneum, which first covers the inferior surface of the diaphragm and the anterior abdominal wall, then reflects onto the superior liver surface meeting the umbilical vein, forms a fold (*suspensor liver ligament)* which spreads from the navel up to the anterior liver edge (umbilical vein channel) and then onto the superior liver surface to the inferior vena cava. This fold creates some sort of an anterior-posterior separating wall, spreading between the diaphragm and the superior liver surface.

After it covers the superior liver surface, the peritoneum surrounds its anterior edge and covers the inferior liver surface and the gallbladder; meeting the hilum organs (branches of the portal vein, hepatic artery, bile ducts, lymphatic ducts, nerves), it covers them and forms another fold (*gastro-hepatic epiploon*) which, to the upper side, starts from the edge of the transversal channel and the Arantius venous channel and reaches, to the lower side, the small stomach curve and the first segment of the duodenum.

The peritoneum segment which covers the superior liver surface develops downwards at the level of the posterior edge and covers the posterior abdominal wall. The part that covers the upper liver surface spreads upwards, towards the posterior edge, so as to cover the inferior diaphragm surface. These two peritoneal foils do not lean on themselves; they leave a space a few centimeters wide, where the liver comes in direct contact with the diaphragm. They form the *coronary ligament*, whose left and right edges, which end in the extremities corresponding to the liver, are called *triangular ligaments.*

The peritoneal liver cover is made, as any serous membrane, of an endothelial foil and a layer of conjunctive tissues underneath it. In the folds or ligaments, this conjunctive tissue becomes fibrous and highly resistant and forms the main instrument by which the liver is fastened to the position it occupies.

The sub-serous tissue, considered a second liver cover, continues to the hilum with the conjunctive tissue which surrounds the branches of the portal vein, the hepatic artery and the bile ducts.

On the microscope, the liver seems to be made of an infinity of similar particles, the *lobules*, which have a venule to the center (branch of the sub-hepatic veins), whose periphery is marked by several portal spaces[2] – vascular fascicles made of the branches of the portal vein, hepatic artery and bile ducts surrounded by conjunctive tissue.

The interior of the lobe, which is the space between the central vein and the peripheral portal spaces, consists of a network of glandular tubes, interconnected with a network of capillaries.

a) The liver is mainly a gland made of ramified tubes which are interconnected. These tubes are formed of hepatic cells with a large ovoid nucleus and abundant protoplasm, which contains protein and fat granulations, as well as glycogen-filled vacuoles.

These cells are juxtaposed and make channels which contain light. The tubes, which are mainly concentrated in the center of the lobe, direct towards the portal spaces and stop at the first excreting bile ducts. Inside the lobules, they seem to connect, making a network with the holes occupied with capillaries. Thus, every tube is separated by a capillary from the neighboring one and we may say that it is surrounded by capillaries on all sides.

b) The last branches of the portal vein end in capillaries which, leaving the portal veins, enter the neighboring lobules. Thus, the last divisions of the hepatic artery creates capillaries which confound with those originating in the portal vein.

All these capillaries draw towards the center of the lobules, between the glandular tubes and reach the original branches of the sub-hepatic veins. On the way, they interconnect and form a highly complex network which crosses the one made of glandular tubes.

Between the intra-lobular blood capillaries and the tubes made of hepatic cells there are virtual spaces which contain a few elements of the conjunctive tissue, which are the origin of the hepatic lymphatic ducts.

Blood vessels and nerves – The liver has two blood circulations: a nutritive one, represented by the hepatic artery, and a functional one, represented by the portal vein.

[2] For Sabourin, the hepatic lobe has a portal space as a nucleaus and a surface which crosses the neighbouring hepatic veins as an edge.

The hepatic artery, starting from the celiac trunk and reaching the liver hilum, divides into two branches which enter the liver lobes and ramify, under the form of a joint conjunctive bag, following the divisions of the portal vein and bile ducts, to which they provide the nutritive branches. The last branches end in the lobule capillary network.

In the liver hilum, the portal vein which carries the blood from the stomach, the intestines, the pancreas and the gallbladder[3] divides into two branches, each entering a lobe and dividing further. Their branches, accompanied by a branch of the hepatic artery and one or several bile ducts, enter the portal spaces. The last divisions turn into capillaries which enter the lobules (see up).

The central lobule veins, which collect the blood carried to the capillaries by the portal vein and the hepatic artery, reunite to form increasingly larger trunks which enter the liver tissue without being surrounded by conjunctive tissue, as was the case with the portal vein. These trunks, generally multiple, but out of which only two reach significant sizes, represent the sub-hepatic veins and open into the inferior vena cava, at the posterior liver edge.

Some of hepatic lymphatic vessels, which originate in the spaces contained between the capillaries and the glandular tubes of lobules, follow the line of the portal vein and reach the liver hilum ganglions; the others, corresponding to the sub-hepatic vein, end in the sub-diaphragm ganglions.

Some of the hepatic nerves originate in the left pneumogastric, while others in the solar plexus. The former, after delineating the small stomach curve, cross the small epiploon and enter the organ through the hilum. Those coming from the solar plexus reach the liver by following the branches of the hepatic artery and the portal vein. The termination of hepatic nerves is unknown.

Bile ducts – The tubular glandular channels that help lobules open into the bile ducts contained in the portal spaces, which unite so as to form increasingly larger ducts and draw towards the liver hilum following the same line as the divisions of the hepatic artery and the portal vein. In the hilum, there are only two large trunks, one for each lobe, which reunite so as to form the hepatic duct.

The hepatic duct, approximately 3 cm long, unites in a sharp angle with the cystic duct with which it forms the choledoc duct.

The cystic duct, 3–4 cm long, has an irregular volume and an internal wall with several valves which separate the widened portions. It contains the gallbladder, with which it communicates through the choledoc.

The gallbladder is a reservoir located on the inferior liver surface, in the duct separating the right lobe from the square lobe, and onto which it is attached and maintained by the peritoneum. It has the shape of a pear; the thick parts or bottom slightly protrude through the anterior liver edge and come into contact with the abdominal wall in the anterior extremity of the tenth right costal cartilage. The peak or cervix, after bending under the shape of an S, continues with the cystic duct. At the junction point, there is a valve which narrows or widens the communication space. The sizes vary depending on whether it is empty or filled with bile. In case of choledoc obstruction, it dilates and can reach enormous sizes.

The choledoc duct, resulting from the reunion of the hepatic and cystic ducts, is approximately 7 cm long. It enters the small epiploon, goes behind the first duodenum curve, enters the pancreatic head, where it comes into contact with the duct of Wirsung onto which it sticks and with which it crosses the duodenum wall. The two ducts open onto a small reservoir, the ampulla of Vater (6–7 mm long and 4–5 mm wide), whose narrowed peak opens into the duodenum[4].

The first bile ducts, located in the small portal spaces, are made of a conjunctive wall lined with a layer of cubic cells, with small nucleus and transparent protoplasm, less abundant as compared to that of hepatic cells.

On larger ducts, the conjunctive wall contains elastic fibers; to the left, the mucous membrane has a layer of smooth longitudinal muscular fibers; it is lined with a cylinder epithelium and diverticula considered glands with mucous. The structure of hepatic, cystic and choledoc ducts is similar. On the choledoc duct, the muscular fibers are increasingly abundant as they approach the ampulla of Vater.

Gallbladder walls are made of an elastic conjunctive layer, covered by a mucous membrane containing folds which delineate the irregular areolas. This membrane is made of a conjunctive

[3] The portal venous system communicates with the general venous system via three main paths: esophageal, umbilical and rectal veins. These veins dilate when the intra-hepatic portal circulation is disturbed, as is the case of cirrhosis.

[4] This space is in the left posterior side of the third portion of the vertical duodenum segment, about 10 cm away from the pillory.

chorion containing intersected smooth muscular fibers; it is covered by cylindrical epithelium and contains glands with mucous.

The gallbladder receives blood from the cystic artery and the veins flow into the portal system.

It has its own nervous apparatus made of ganglionic cells which innervate the muscular mucous fibers and those of the blood vessels. This apparatus is connected to the solar plexus through fibers which follow, most of them, the trajectory of the cystic artery.

The same can be said about the innervation of the hepatic, cystic and choledoc ducts.

We should add that all these bile ducts have a significant innervation emphasized by the hepatic colic.

Physiology – The liver has two main functions:

1. to cause transformations of certain food substances which it renders assimilable by tissues;

2. to excrete the bile.

1. During digestive absorption, the portal vein blood receives albuminoids and glucose.

a) The liver receives albuminoids, maybe some fats as well, originating in the intestine which sets them under a form which is not very well known and reinserts them in the circulation after turning them into protein substances and fats which are normally found in blood.

b) The liver stops the passage of hydrocarbonated substances and binds them to its cells. It particularly stops the glucose and, through a mechanism which is still unknown, dehydrates it and turns it into glycogen which is stored in the protoplasm of its cells. Glycogen binding inside the liver can be assisted by the internal pancreatic secretion; this intervention is less visible when glycogen is bound in the muscular fibers.

The amount of glycogen contained by the liver varies within wide ranges; on average, it is 3 or 4 to 100 and it can reach 10 to 100 and more, after a meal rich in carbohydrates. This ratio decreases considerably and can reach the zero level after prolonged fast, flu or strenuous muscular activity.

Hepatic glycogen[5] is then retransformed into glucose by special diastasis produced by the hepatic cells, diastasis which is destroyed through boiling. The resulting glucose is taken over in the blood depending on the needs of the organism.

The hepatic transformation of the glycogen into glucose is, up to a point, dependent on the nervous system.

A puncture of the fourth ventricle, on the median line (between the nuclei of the acoustic and the pneumogastric nerves) generates hyperglycemia and glycosuria (Cl. BERNARD), phenomena which slow down when the hepatic glycogen reserve is exhausted and missing in animals whose liver was devoid of glycogen by prolonged fast.

It was proven that these phenomena do not occur when the splanchnic nerves are previously sectioned and, as we know that the bulb puncture generates abdominal vasodilation, the conclusion is, until further data, that bulb puncture produces liver vasodilation following the vasomotor inhibition of this organ which is transmitted by the splanchnic nerves[6]. This hepatic vasodilation would lead to an excessive glycogen transformation and subsequently, to hyperglycemia accompanied by glycosuria.

In fact, any bulb excitation, for instance, the excitation resulting from suffocation or hemorrhagic anemia (syncope) can cause hyperglycemia and glycosuria through a similar mechanism.

The arterial blood contains a constant ratio of glucose (1 g to 1 g 50 per liter) consumed by the tissues, since venous blood contains less glucose than arterial blood.

Blood glucose comes from the glycogen stored in the liver, which largely derives from the food carbohydrates absorbed in the intestine; in fact, during food absorption the blood of the portal vein and that of sub-hepatic veins contains more glucose than arterial blood.

Some authors have tried to demonstrate that the organism can produce glycogen not only with carbohydrates, but also with albuminoids; the liver contains glycogen even when carbohydrates are excluded from the diet.

On the other hand, it has been set that the organism can still produce glucose when all the glycogen disappeared from the liver, for instance, following prolonged fast; under the circumstances,

[5] The glycogen, which is not dialyzable, represents the fix form of carbon hydrates, whereas the glucose, which is dialyzable, is their circulating form. Pneumogastric excitation generates hypoglycemia.

[6] Pnenumogastric excitation generates hypoglycemia; therefore, we can accept that these nerves contain exciting fibers for the hepatic vasomotor nerves, the inhibiting fibers being contained in the splanchnic nerves.

Some authors believe that the effects of sections and excitations of the splanchnic and pneumogastric nerves on the transformation of glycogen into glucose are independent of any circulation modification; thus, they call the former nerves glyco-forming nerves and the latter glycol-phrenic nerves.

the sugar ratio in the arterial blood does not decrease significantly.

It is also known that some patients with diabetes eliminate a considerable amount of glucose even when their diet does not contain carbohydrates.

Still, it has not been rigorously proven that the organism has the ability to turn, if it needs, albuminoids into carbohydrates: glycogen and glucose. There is also no fact which demonstrates the production of these substances from fats.

This observation shows that the glucose ratio in the arterial blood remains constant despite the intermittence of the food intake and tissue consumption. This happens because there is a glycemic regulation apparatus, under the influence of which the liver binds the food sugar under the form of glycogen and sends it to the blood retransformed into glucose, pro rata with the amounts consumed by the tissues.

This apparatus is made of the *hepatic-pancreatic* and the nervous system.

The experimental research of one of us seems to reveal that the product of internal pancreatic secretion plays an important part in binding the glucose, the blood in the portal vein as glycogen in the liver. This prior binding seems to be absolutely necessary to allow the sugar to be assimilated by tissues. In fact, in case of pancreatic insufficiency, the liver does not bind the glucose as glycogen[7]; thus, the sugar, which is imperfectly processed and incapable of serving tissue nutrition, accumulates in the blood and, if it exceeds the ratio 3 to 1000, it is eliminated through the urine as a foreign body.

It is common knowledge that, in animals which suffered from partial pancreas extirpation, glucose appears in the urine whenever they absorb rapidly a large amount of sugar, amylacea as if, under the circumstances, their liver were not capable to bind the entire amount of glucose coming from the intestine.

In animals completely deprived of pancreas, glycosuria occurs not only after a meal rich in carbohydrates, but even in the case of a diet made exclusively of fats and albuminoids and even in the absence of any diet. In this case, the organism can no longer assimilate the glucose, whether it comes from food carbohydrates, albuminoids or from the protein substances entering the composition of the tissues.

[7] Recent research has shown that, under similar conditions, the liver can bind laevulose as glycogen.

II – *The bile,* contained in the gallbladder, is a flowing transparent viscous liquid, yellowish-brown in color, lighter or darker, which, in contact with the air, acquires a greenish hue. It has an alkaline reaction and density of 1020–1040; the amount produced in 24 hours averages 500 ml.

As for the chemical composition, the bile is made of a certain part of water in a solution:

a) of mineral salts, chlorides and phosphates, alkaline and alkaline-earth metals;

b) a substance which gives the bile its viscosity and which precipitates through the acetic acid and alcohol similar to mucin; it is distinct due to other features which make it more similar to nuclear albumins;

c) traces of lecithin, neutral fats, soap, urea;

d) cholesterin[8], which enters the composition of most bile calculi;

e) bile salts and pigments, characteristic substances which are only found in the bile.

Bile salts are the glycocholate and the sodium taurocholate. They are found in the bile in a proportion of approximately 10%, almost three quarters made of glycocholate and only one quarter of taurocholate. Soluble in water and alcohol, they are indissoluble in ether, which allows their separation and dosage.

When treated with a mineral acid, these salts release bile glycocholic and taurocholic acids, the former made of a non-nitrate organic compound, the cholalic acid, combined with glycine (amino-acetic acid) and the former from the same cholalic acid, combined with taurine (a sulphur-containing substance).

The presence of bile salts and acids in an organic liquid can be demonstrated through the *reaction of Pettenkofer.* If we place in a china dish a drop of bile liquid, a drop of sulfuric acid and a drop of sugar syrup and we slightly heat the mixture, we notice a beautiful specific red color[9].

[8] Cholesterine is also found in nervous centers and in egg yolk. The physiological significance of this substance is unknown; it is only known that it has a chemical function of primary alcohol and when combined with fatty acids, it forms cholesterine fats (lanoline) which are found in the sebum.

[9] This color appears after the contact of the cholalic acid with the furfural, which results from the action of the sulfuric acid on the sugar.

Bile pigments are bilirubin and biliverdin[10], acid compounds which are found in the bile as potassium and sodium bilirubinates and biliverdinates.

Biliverdin and biliverdinates are oxidation products of bilirubin and bilirubinates. They are formed when the bile extracted from the gallbladder is left in contact with the air.

In the presence of reducing agents, bilurbin and biliverdin turn into hydrobilirubin or urobilin.

The existence of bile pigments in an organic liquid can be demonstrated through the *reaction of Gmelin.* If we put in a glass first nitric acid (oxidant agent) and then some liquid which presumably contains bile, we see at their separation line a series of areas colored yellow, red, violet, green and blue, corresponding to the increasingly oxidized bilirubin derivatives.

In old hemorrhagic foci, we find a substance, hematoidin, derived from hemoglobin, which presents all the features of bilirubin: we draw the conclusion that the bile pigment is also the result of a hemoglobin transformation in the blood. In fact, it is common knowledge that a blood peritoneal or subcutaneous injection, just like an intravenous one with hemoglobin or with a substance dissolving the red cells (for instance, toluilen-diamine) leads to the increase of the number of pigments in the bile.

According to some authors, the spleen would play a significant part in turning hemoglobin into bilirubin. PUBLIESE, CHARRIN and MOUSSU believed to have noticed the fact that spleen ablations would lead to bile discoloration. But experimental research carried out by one of us with a more rigorous method revealed that splenectomy does not modify bile secretion[11].

It seems that bile salts and pigments are produced by the hepatic cell, since they are not found in blood under normal conditions.

The bile is secreted by the liver continuously, even during starvation periods, as indicated by its draining through a gallbladder fistula. Its amount[12] is, up to a point, related to the amount of blood crossing the liver. It decreases following abundant hemorrhage, an obstruction of the hepatic artery, a circulatory disorder in the portal vein and the hepatic veins[13].

If bile secretion is continuous, its excretion is *intermittent*[14] and only occurs during gastric digestion. It starts about half an hour after the meal, lasts as long as the food stays in the stomach and ends about 5–10 minutes after the chyme exhaustion in the duodenum.

During digestions in fasting periods, the bile does not drain into the intestine, but gathers in the gallbladder.

Bile excretion is a reflex phenomenon which seems to be caused by the contact of stomach and duodenum mucous membranes with fat substances and chyme proteases. It is admitted that the impression resulting from this contact is sent through the pneumogastric nerves to the bulb which reflects it through the splanchnic nerves, determining the gallbladder contraction and the relaxation of the choledoc sphincter.

The physiologic significance of the bile has not been completely clarified.

The fact that it does not contain soluble ferments capable to act on food substances and that its secretion starts in the third month of intrauterine life seem to indicate that the bile is only an excretion product.

On the other hand, it is clear that it has a significant role in the intestinal absorption of fats and, in case of complete obstruction of the choledoc, the absorption of these substances is considerably lowered[15].

Some experiments determine us to admit that the bile favors the action of pancreatic steapsin[16].

[10] Bilirubin is soluble in chloroform, whereas biliverbine is insoluble, which allows the isolation of these substances and obtaining them in pure condition from any mixture.

[11] Paulesco, C.R. *Acad. des Sciences, 1905; Bull. Acad., Médecine, 1906; Journal de physiologie et de phatologie générale,* 1906.

[12] The bile introduced in the intestine of an animal causes an increase of bile secretion in the animal; it is said that the bile is a *cholagogue.* This name has also been applied to several substances, calomel, among others, whose action on bile production is still not clear.

[13] This proves that bile secretion does not depend only on blood pressure in hepatic capillaries, since this pressure considerably grows when hepatic veins are obliterated.

[14] The study of bile excretion was made on animals with the help of the fistulae of Pavlov (resection and binding to the skin of a small portion of the intestinal wall containing the ampulla of Vater), which keeps the choledoc sphincter intact.

[15] Fats are absorbed, at least partially, when they have the form of fine emulsion similar to milk.

[16] In rabbits, the excreting pancreatic duct opens onto the intestine about 30 cm below the choledoc. After a meal made of fatty substances, the chylophoric vessels originating in the intestine fragment where there is nothing else but bile are slightly less white than the ones created above the point where the bile mixes with the pancreatic juice.

Similarly, in a dog, whose choledoc was tied up and the gallbladder was connected directly to the intestine, a few centimeters above the orifice of the duct of Wirsung – the chylophoric vessels coming from the intestine where there was

In the intestine the bile quickly suffers profound changes. Bile salts are partially reabsorbed; the rest is decomposed and goes into the feces, where there is a small amount of cholalic acid. As regards bile pigments, partially turned into urobilin through microbial fermentation, they are eliminated with the feces, to which they give their initial brown color; it is known that, in case of choledoc obstruction, the feces suddenly become white.

III – The liver also has two other functions:

a) to turn amino acids, ammoniac salts and uric acid and xanthic base into urea, all substances resulting from the lack of assimilation of albuminoids and nuclear albuminoids in the organism;

b) to neutralize certain toxic substances that entered the blood via the intestine; thus, poisons and some drugs, when injected subcutaneously at a lower dose have the same effect as when ingested.

MEANS TO EXPLORE THE LIVER

For a thorough liver examination, the following operations must be performed:

a) *Inspection* must begin through analysis of the right hypochondrium, then of the entire abdomen. This exploration shows if there is any smaller or larger curve or protuberance of the hepatic region. It also indicates whether the abdomen is excessively developed in the upper side (meteorism) or if it has the shape of a batrachian abdomen, which is sunk in the middle and deformed at the extremities (ascites); if the abdominal subcutaneous veins are dilated and visible; if there are any hernias, especially umbilical; if the liver has pulsations synchronous with the systole of the right ventricle.

b) *Auscultation* provides only very limited data such as: friction noises and agitation in case of perihepatitis or a clang when there are gallbladder stones.

c) *Percussion* is the examination method which is used for the liver by excellence.

The patient lies down on the back, on a slightly reclined or horizontal plane; s/he relaxes the abdominal muscle, slightly separating the knees and bending the legs towards the thighs.

The doctor sits to his/her right and executes the percussion, up-bottom, on three lines: median, mammal and axillar.

This percussion must not be practiced identically in all cases.

In order to delineate the upper limit of the liver, which is the segment covered with a blade of the lung and the diaphragm, an *in-depth percussion* must be carried out, since the doctor is interested in hearing the sound of the profound organ.

But in order to delineate the anterior edge of the organ, especially if it exceeds the coastal margin, the percussion must be made *weakly and horizontally*, with the fingers hitting a very oblique plane (light percussion); the doctor is interested in hearing the sound of the superficial organ and, unless this condition is complied with, the sounds will come from the stomach or the neighbouring intestine, which falsifies the exploration results.

The superior liver limit does not generate clear dullness, but only a delicate sound, distinct from that of the lung, which is also recognized through a decrease of elasticity under the percussion finger. On the contrary, the anterior limit of the organ is identified due to a blunt sound distinct from the gastro-intestinal sounds underneath. Between these two limits, as we move downwards, we must decrease the percussion force.

By proceeding this way, we realize that, in healthy persons, the upper limits of the liver are relatively fix. On the mammal line, this limit is located in the 4^{th} intercostal space and, sometimes, it goes up to the 4^{th} rib or down to the 5^{th}; at any rate, it is located at one or two finger widths under the nipple. On the axillary line, it corresponds to the 7^{th} rib and, close to the spine, to the 10^{th} rib. If we draw an imaginary line from the 4^{th} intercostal space to the head of the heart, we obtain the superior liver limit on the median line and to the left of this line which it exceeds by 7 centimeters.

The anterior liver limits are less constant. Generally, this organ barely exceeds the coastal margin at the level of the mammal line and, on the median line, its edge goes slightly above the middle of a line uniting the xyphoid appendix with the navel.

These reports consider an adult male; in children, the left lobe is larger than at a more advanced age. In women, the upper limit is similar

no pancreatic juice are significantly less injected that those originating under the level where the two secretions mix (DASTRE).

In the presence of fats and mainly fatty acids, the bile generates soaps. We wonder whether it is not here that we may find the key to the bile influence on pancreatic fat digestion, soaps serving to produce emulsions that considerably facilitate the steapsin action.

to that of men, but the lower one is less prominent because of the smaller height of the thorax and the deformation caused by the corset.

d) *Liver palpation* is just as important; it is associated with the percussion, which it completes.

The patient must lie down, knees separated and legs slightly bended towards the thighs in order to completely relax the muscles of the abdominal wall.

The doctor, to the right of the patient, touches the abdomen with the palm, above the navel and invites the patient to take a deep breath; then, with each exhalation, he strongly presses the abdomen wall and runs his hand bottom-up until he reaches the clear liver edge which the fingers can feel if the wall is sufficiently thin and relaxed. At this moment, it is easy for him to follow the edge on its entire length, to realize the width, toughness, unequal parts, deformations and to draw the edge on the wall with a pencil.

The surface of the organ is felt with the palm as well, pressing the abdominal wall during exhalations; thus, the doctor can feel the frictions, irregularities, cancerous nodules and even cirrhotic granulations; with some practice, the doctor can even recognize the degree of softness or toughness of the parenchyma.

We should mention that liver palpation is more difficult in obese persons.

Another palpation procedure consists of picking the lumbar region with the last 3 fingers of the left hand, trying to feel with the big finger the liver edge by pressing with the right hand (GLÉNARD).

Exploration is also possible with one hand, which placed on the back, imprints a shock to the liver which is transmitted to the other hand which is placed on the front. Thus, we can recognize liver mobility and, thus, the adherences it has either with the organs or with the neighbouring neoplasms.

Liver exploration also involves the examination of the feces (p. 930) and of the urine, especially with respect to the bile elements they contain (the reactions of Gmelin and Pettenkofer).

HEPATIC SYNDROMES

JAUNDICE

Jaundice is characterized by the yellow coloration of the skin, caused by the presence of the bile in the blood and tissues.

Etiology and pathogenicity – Jaundice is either the effect of an obstacle in the bile drainage to the intestine or of an alteration with destruction of the hepatic cells.

It is caused either by various agents which obstruct the bile ducts (calculi, neoplasms etc.) or by various disorders causing lesions of the hepatic cells (phosphorism, alcoholism, various fever types etc.).

In the former case, bile absorption occurs particularly in the large bile ducts; in the latter case, this liquid is resorbed in the hepatic lobe on the path of lymphatic vessels, which form some sort of cover around the capillaries and thus create the connection with the glandular cells.

In both cases, the bile rapidly enters the blood and colors the serum greenish yellow (cholemia). It is carried by blood to various parts of the body, where it undergoes extravasation with capillaries and the coloring matter impregnates the tissues.

These acquire a pale yellow hue in case of hepatic alterations and a lighter or darker yellow color up to green and even black in cases of bile obstruction.

Pathologic anatomy – Initially, the bile absorbed by the organism following an obstruction of the bile ducts only has the effect of coloring the tissues and the liquids. After a while, it irritates and alters the cells with which it comes into contact.

Hepatic cells are impregnated with pigments and, later one, fill up with protein or fat granulations. The same happens to the cells of the kidneys, whose urinary tubes end up by being obstructed by yellowish cylinders; in this case, the urine contains albumin.

In a more advanced stage, the blood and the circulating apparatus suffer from less studied alterations which cause multiple hemorrhages.

Muscular fibers, similar to nervous cells, are less affected by jaundice. The same happens to sense organs; thus, the eye liquids are rarely colored in yellow. However, sometimes there is a feeling of rash, bitter taste, xanthopsia, which indicate that peripheral portions of these organs are affected by jaundice.

Symptomatology – The yellowish jaundice coloration through bile retention is immediately noted in sclerotic patients, whose white complexion immediately turns yellow.

With a more intense bile concentration, the yellow hue also appears on the skin, since the cells of Malpighi impregnate with the pigment. This hue is first noted on the spots where the epidermis is thinner, on the nostrils, around the mouth edges, on the forehead and throat.

Initially, it is a pale or sulphur yellow; subsequently, the color darkens, intensifies and acquires a greenish or brownish hue, while the bilirubin oxidizes and turns into biliverdin. The skin color in jaundice is darker in older and thinner persons. In the same individual, it can vary in terms of intensity, depending on the diet, amount of bile secreted by the liver, kidney activity. It persists for a while after the bile obstructions ends.

The bodily liquids are also colored by the bile. The tears, the perspiration, the milk, all contain coloring bile matter; these liquids are yellow and can easily stain the bed cloths.

Urine in particular contains bile elements, since it has the role of eliminating them. Usually little abundant and with high density, it successively acquires an intense yellow, brown, greenish brown or black color as the concentration of the pigment grows. At the beginning of jaundice, it colors before the sclerotic membranes and the skin; in some cases of temporary retention, the bile pigment contained in the blood can be eliminated through the urine without coloring the skin considerably.

The coloring bile matter impregnating the teguments causes in about one fifth of the cases, a rash which affects the patients and prevents them from sleeping. The skin shows traces of scratching which can infect and generate furuncles; sometimes, it becomes the spot of papular eruption or urticaria. This rash sometimes ends even if the intensity of jaundice grows.

Patients continue to be rarely discomforted by a bitter taste; they also complain that they see yellow (xanthopsia).

Finally, in some jaundice cases, there is an eruption of *xanthelasma*, which consists of isolated or clustered tubercles, with the volume of a lentil grain, smooth, yellowish, on the face, ears and more seldom on the limbs, buttocks, scrotum et. These tubercles are made of a fibrous tissue, impregnated with an opaline liquid which contains fat globules and radiated acicular crystals.

Besides these phenomena related to tegument jaundice, the presence of the bile in tissues determines several types of disorders.

Often, heart beats slow down, which is caused by the presence of bile salts in the blood. The number of heart pulsations drops to 50 or 40 a minute, even less. This condition can extend for several weeks; it is replaced by a certain pulse frequency, if fever occurs.

The appetite decreases or is lost completely; digestion becomes slow; the intestine, deprived of bile, meteorizes following fermentations; the feces lose color becoming grey or whitish, viscous, rich in fat matters and with a repugnant odor. When they acquire color again, it is a sign that the bile ducts are no longer obstructed, which precedes healing by little.

Patients become more and more anemic and lose weight increasingly.

Jaundice has a continuous and progressive development. Its duration varies with the bile obstruction; very short in certain cases of hepatic colic, it can be extremely long when a calculus is blocked in the choledoc, when there is cancer of the pancreas or bile ducts, when these ducts narrow down.

Semiology and treatment – Jaundice is easily recognized. When it is very dark, it can be mistaken for melanodermia, but it is enough to examine the urine to avoid this mistake.

The prognosis is not serious unless jaundice prolongs and is accompanied by signs of hepatic insufficiency.

Jaundice treatment varies depending on the causes leading to the obstruction of bile ducts (calculi, neoplasms, narrowing). Kidney functioning must be monitored and activated, if necessary, through diuretics or purgative supplements.

Besides bile jaundice, there are other hepatic disorders (active and passive congestions, alcoholic and especially paludic cirrhosis), *a yellowish tanned coloration* of the skin and sclerotic membranes, which is distinct from the real jaundice through the fact that the urine does not contain bilirubin. This condition was called *hemapheic jaundice* by GUBLER, who erroneously attributed it to an excessive destruction of red cells. HAYEM calls it *urobilinuric jaundice* and believes that it results from the blood accumulation of urobilin and a brownish red pigment deriving from it.

In paludic cirrhosis, where this color of the skin is highly intense, it seems to reveal, as we noticed many times, a considerable bile abundance (polycholia) which acquires a dense consistency,

almost semi-liquid, and barely crosses the bile ducts. This bile is obviously altered.

This form of jaundice translates into a tanned yellow, brown or black hue of the skin, whose intensity varies depending on the free drainage of the bile in the intestine or accumulation in bile ducts. It does not generate any other appreciable phenomenon; however, it is sometimes accompanied by *hemeralopia.* The feces are usually intensely colored; they become lighter when the bile accumulates in the excreting ducts. The urine, which is reddish yellowish and lighter or darker, does not produce, when treated with nitric acid, the green hue specific to the bile pigment; at the limit between the two liquids there is an area colored in dark red.

This condition is easily recognized; it is distinct from bile jaundice dues to the absence of bilirubin in the urine.

The prognosis is benign, since, against the general belief, it does not reveal a destruction of hepatic cells. In paludic and enological cirrhosis, this syndrome is noticeable from the very beginning, when the hepatic cells are slightly altered or completely unaltered; in the final stage of hepatic insufficiency, when the hepatic cells are largely destroyed, this condition is replaced by real bile jaundice.

The treatment of this type of jaundice is similar to that of causal disorders.

HEPATIC INSUFFICIENCY
(Syn. *Serious symptomatic jaundice*)

When the hepatic cells are altered or largely destroyed, a new syndrome occurs, *hepatic insufficiency,* which manifests through disorders of the liver functions and the general positioning of the body. This condition is comparable with uremia or renal insufficiency, which, more often than not, follows the alteration or destruction of kidney cells.

Etiology and pathogenicity – Hepatic insufficiency, rarely caused by a mere nervous disorder, usually occurs during a disorder of the liver produced by a toxic agent (phosphorus, arsenic, alcohol, wine), microbes (eruptive fever, yellow fever, serious jaundice), neoplasias, obstruction of bile ducts etc. It manifests in an advanced stage of these disorders, always when the hepatic cells suffer from profound alterations or are destroyed.

The process of this syndrome is highly obscure, given the knowledge we have of the hepatic functions. The liver, altered or partially destroyed, can no longer retain and process the food substances provided by the intestine so as to make them easy to assimilate; therefore, general nutrition is affected. At the same time, destroyed cells abandon, among others, the bile elements which are taken over by the lymphatic vessels and, once they reach the blood, they generate mild jaundice. Since the bile is no longer secreted as usual both quantitatively and qualitatively, certain principles, such as oleates, do not suffer changes that neutralize their harmful activity and generate hemolysis. Other substances, still little known, act on the walls of small vessels and cause multiple hemorrhages. Finally, general nutrition is disturbed and the results are toxic principles which attack the nervous system and cause delirium, somnolence, coma followed by death.

Pathologic anatomy – The liver is pale, yellowish, similar to tobacco; it is soft and lax. The bile is little abundant and often almost discolored. Hepatic cells are granular and the nucleus does not bind well the coloring matters. The spleen is often tumid. The kidneys reveal alterations similar to those of the liver; they are soft, friable and their cells are affected by tumefaction.

Symptomatology – The beginning of hepatic insufficiency is usually slow and insidious; other times it can be obvious and sudden.

It starts with digestive disorders; the appetite drops and soon is completely lost; then lack of appetite is completed by repulsion and disgust for food, especially fat. Then there is flatulence, meteorism, constipation, all related to bile reduction; the feces are pale or almost discolored, grey, clay-like and excessively fetid. In some cases, greenish diarrhea occurs. Other times, little abundant bile or mucous nausea and vomiting and ascites with dilation of the subcutaneous abdomen veins occur. General nutrition is slow, albuminoids and especially glucoses are no longer stored by the liver (food glycosuria). At the same time, patients rapidly lose weight and can become excessively emaciated.

Jaundice occurs simultaneously; it is very mild and only limited to sclerotic vessels or colors the skin in pale yellow; this form of jaundice, which is accompanied by the presence of the bile in the urine, differs from bile retention jaundice, besides it

slow intensity, through the fact that the feces are not fully discolored. Rare urine often presents the reactions of Gmelin and Pettenkofer; it contains urobilin, a brownish red pigment, very little urea and uric acid and sometimes albumin.

Hemorrhages, most of them associated with jaundice, soon follow; they represent a highly significant symptom, since they occur when the hepatic cells are really affected. Epistaxis is one of the most frequently met; it is followed by stomatorrhagia, hematemesis, melena, purpura, petechiae, cutaneous bruises, and, more rarely, hemoptysis and hematuria. These hemorrhages, which most often start on the nose, repeat at shorter or longer intervals; then, after a while, they occur simultaneously in several points and simulate hemophilia.

In a more advanced stage, *nervous disorders* complete the series of symptoms. They consist of a general feeling of exhaustion, muscular pain and difficulty to move in bed; the patient is sad, irritable, prey to general weakness with anxiety and feeling of oppression; he has headaches, dizziness and persistent insomnia, with moans once he falls asleep, which lead to delirium. Initially it is calm, with incoherent words and visual hallucinations. Then, the patient often moves to active delirium; he fumbles for imaginary objects and tries to pick them up and leave the bed; if he succeeds, he urinates on the furniture or goes to sleep in another bed. Sometimes the agitation increases and delirium turns into *hepatic lunacy*.

Delirium is followed by somnolence and adynamia, which soon turns into a coma with or without the contraction of the jaws, muscular movements, convulsions or paralysis.

The pulse is frequent and filiform; breathing is abdominal and slow; temperature drops under the normal limits; the tongue dries and turns blackish. Finally the patient dies.

The syndrome evolution is continuous and progressive; sometimes it stops, even in the coma, under the influence of a diarrhea or vomiting crisis. The duration, several days sometimes, prolongs other times for several months. The end is usually fatal.

Here is a personal case study as an example of hepatic insufficiency. A commissioner of a wine merchant, aged 49, had been hired by a distiller since the age of 10. He has been making deliveries to 30 or 40 wine merchants a day and almost all of them offered him one-two glasses of wine; which means that he drank enormous amounts of liquid for about thirty years. He had been drinking less for the past four to five years; but he reached 3 or 4 liters of wine a day. His general condition was good, although he had been suffering for a long time from pituitary disorder, sleep disturbed by horrible nightmares, cramps and intense tingles in the legs.

A year before, he had lost appetite; them he acquired a disgust for fat food. At the same time, he started to lose weight, while the abdomen progressively swollen. For two months, the sclerotic membrane acquired a yellowish hue and had several highly abundant crises of epistaxis.

He was hospitalized and he presented mild jaundice; his intellectual abilities weakened; the pulse, strong and regular once, was 100. He had meteorism, mild ascites with dilation of abdominal subcutaneous vessels and edema in the legs. The liver and the spleen were large. The feces were slightly colored and the urine rare, acid, dark red, with the density 1022, contained 22 gr. urea every 24 hours and did not contain any sugar or albumin; the additional nitric acid caused the production of an abundant brown red pigment. The temperature was under the normal limits. At night he was agitated and wished to stand up and leave.

A few days later, the temperature increased to 38°, 39° and 40°. One morning, the patient failed to recognize the persons around him and continuously mumbled incoherent words; the mouth was half opened, the tongue dark and the lips dry; the muscles were very painful. Urine exam revealed the presence of a small amount of glucose.

An injection of 700 ml artificial serum caused, during the night, an emission of urine so abundant that the bed was entirely wet. The next day, he had a livelier look, he recognized the persons who talked to him and answered the questions pretty coherently. But it was just a transient improvement. He continued to lose weight, lost consciousness again and died in a coma, with 40° temperature.

The necropsy revealed, besides the pneumonia of the right lung lobe, a liver affected by enolic cirrhosis, with a slightly increased gallbladder by a turbid and slightly colored bile, as well as a very large spleen.

At the microscope, the hepatic ducts were some transformed into excreting bile ducts and other fragmented and their turbid cells impregnated with fat could hardly absorb the coloring substance.

Semiology – Hepatic insufficiency is characterized by symptoms and coexistence with a

serious liver disorder. Easily recognized in phosphoric poisoning, yellow fever, it is more difficult to detect in eruptive fever or cirrhosis, where it is often complicated by alcoholic or uremic accidents.

The prognosis of this syndrome is very serious; it is much more serious than uremia, since we can cure renal insufficiency more easily than hepatic insufficiency.

Treatment – Since no other organ can replace the liver, the first indication in case of hepatic insufficiency is to act on the kidneys and the intestine so as to cause the elimination of toxic substances poisoning the organism. Diuretics and cholagogue purgatives must be administered in sufficient dose. Messages are very effective as an excitant of skin functions. Insomnia and delirium shall be treated with chloral, opium being dangerous because of the tendency of coma it produces. The patient shall follow a strict diet consisting of milk, simple or with addition of alkaline water, coffee or brandy.

To be continued in next issue…