Acute Yellow Atrophy of the Liver.

Atrophia Hepatis Acuta Flava.*
(On the basis of experimental data.)

Dedicated to the memory of late Professor P.S. Ikonnikoff.**

By

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INTRODUCTION.

In the twentieth century a new function of the digestive apparatus was discovered—the periodical secretion of the pancreatic

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* At the present I am deprived of the opportunity to carry out some simple experiments which would prove the correctness of my views in this article. I have first expressed my views on the subject in 1928, in separate chapter in a large article published in the Ergebnisse d. Physiologie in 1929. I have later taken out this chapter fearing that the readers may reprove me for lack of sufficient experimental material, although I was convinced in the truth of my conclusions even then. But other people would require experimental proofs. I hoped it would be easy to obtain these, and I began working on this problem with the collaboration of Dr. A. H. Kretchmar. However, unfortunately, these experiments were not completed and I do not know when I may have the opportunity to resume them. The time draws short and it would be a pity if my data on the acute yellow atrophy of the liver, which are of some value, should get lost. For this reason I decide now to publish them without additional experimental proof.

** P.S. Ikonnikoff was an exceptionally gifted surgeon and a scientific worker of unusual ability. It was a great pleasure for me to work in collaboration with him. He was also a rarely kind and successful physician. When in some large surgical clinic some doctor wished to get off his hands a patient whom he thought to be a hopeless case, Ikonnikoff would take charge of the case and almost without exception saw it through to complete recovery. Going to the front in 1914 as a volunteer, he overworked himself, operating practically all day long, often even through the night. He undermined his health and died a victim of acute yellow atrophy of the liver in December 1914. He was greatly beloved by his patients and his colleagues for his genial nature and his desire to be of help to everybody. But he never took care of himself, giving everything to others. His memory will never leave the hearts of those who were fortunate enough to associate with him. His scientific and medical works are a perfect illustration of the high standard of his gifts, of his excellent erudition and skill as a physician and a scientist. His death was a heavy loss for medicine and science.
juice. This is the real basis of what is usually understood as the “internal secretion of the pancreas.”

In this article I have no space to discuss in detail this very important physiological phenomenon. This has been done in my papers in the following publications: Arch. de Phys. et Path. Gen., 1902,1 Arch. de Science Biol., 1905,2 Revista Pasteur, 1908,3 Ergebn. der Physiol., 1911 and 1924,4 Quart. Jour. of Exper. Phys., 19165 Bull. of Battle Creek San., 1928,6 Am. Jour. Digest. Diseases and Nutrition, 1934.7 It would be more interesting and more instructive for the practicing physician to learn of the pathological states which may be due to a disorder of this function.

As in other instances, such as affection of the thyroid gland, two kinds of diseases are possible—1. those caused by hyperfunction, and 2. those depending upon hypofunction of the named organ, likewise in the affection of the pancreas, we meet diseases which are traced to hyperfunction of the pancreas—sea sickness, atrophy of the liver, hyperemesis gravidarum, and with diseases which are consequences of pancreatic hypofunction—diabetes mellitus and haemophilia. I had the honor to make a report on sea sickness in Paris in 1926, at the congress of French physicians. Atrophy of the liver is the subject of the present article. And references to the last named two diseases may be found in the current medical literature (Acta Med. Scand., 1934,8 Am. Jour. of Dig. Dis. and Nutr., 1935,9 Tohoku Jour. Exper. Med., 1936,)10

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I.

General Data on the Disease.

Acute yellow atrophy of the liver, as one readily sees from the very name of the malady, consists in a rapid decay of liver cells which involves at first a weakening and then a complete arresting of the liver function with all natural consequences.

This disease has been known since ancient times and carefully studied but its etiology remained enigmatic up to the present time. Yet, some authors (Henoch, Bouchard) have offered an explanation of its etiology coming very close to the truth, although they were unable to prove the correctness of their findings.
It is fortunate that this disease is comparatively rare, but on the other hand it is incurable and results in a rapidly coming death. There is little of importance, and of firmly established fact, that could be added to the scant above statements.

Rokitansky has discovered presence of bile in the blood of the patients afflicted with this malady; Frerichs found leucin and tyrosin, later lycin has been found in the blood of such patients.

Also was noted fatty degeneration and autolysis of the cells of the liver, cardiac and skeletal muscles, and kidneys. Hemorrhages in various organs were observed, indicating a lesion of the blood and blood vessels. In the urine, along with a decrease in urea some albumose, peptone and some amino-acids were found in abundance.* This is all, that is essential, from the physiological point of view.

Apparently, there is an autolysis of the specific cells of tissues in the liver and other named organs, but its causes and its mechanism remain a riddle. It is also an unsolved problem why women are more frequent victims of this disease than men and why pregnancy predisposes them to it.

Let us make an attempt to explain the causes for, and the essential points of, the acute yellow atrophy of the liver, in the light of our long published data on the periodical activity of the digestive glands which are little understood and poorly assimilated by physicians.

But first, we take pleasure in stating that two authors, Henoch and Bouchard, have already expressed correct ideas in regards to the etiology of this disease although they could not prove their views. The first man thought that the autolysis of liver cells is effected by the bile; in reality it is effected by the pancreatic juice, which, as we shall see below, is closely related. The second man considered that the disease was due to autointoxication from the bowels, which is quite true, although rather indefinitely expressed by him. However, no one could give more exact explanation for lack of information in the physiology of digestive apparatus, which we have accumulated much later.

* The central nervous system is strongly affected by some poison. One is amazed by a peculiar "jaundice," while the bile ducts are passable and the gall bladder is empty.
II.

The True Essence of the Disease.

There is no doubt whatever that the acute yellow atrophy of the liver is caused by the autolysis of liver cells. This is the real root of the disease, its first cause. All other manifestations follow from it.

But what causes the autolysis? And how is it effected?

Probably all would agree that autolysis consists in autodigestion of liver cells by some ferments. Now it remains to discover their source and to establish their nature.

In my former publications I have shown that the so-called intracellular ferments, capable of digesting proteins, fats and carbohydrates in any organ and tissues of the body, are not formed by the cells where we see their work, but are carried there by the blood stream from the digestive apparatus. There are the same ferments which take part in digestion and splitting all kinds of food, and which are later absorbed into the blood. I have many times described their intracellular work in normal conditions. The first place among these ferments is occupied by the pancreatic ferments; then follow the intestinal; pepsin (or rennin) plays no role here.

Now we must talk about the pathological role of these ferments.

I must remind the reader that the named ferments enter the intestine and then are absorbed from there into the blood, not only during digestion, but also outside of it. In the latter case they are even much more noticeable since in absence of digestive work they are free and therefore can better develop their other activity. Also absorption is quicker from an empty bowel. I named the pancreatic and intestinal juices; there is little question of bile for it usually is devoid or nearly devoid of ferments, it served merely as activator of pancreatic lipase. These juices are secreted into the empty intestine, outside of digestion; I called them “periodical,” because they enter the intestine periodically, with regular short intervals of time. In man approximately about every 1 or 1½ hours.

Periodical juices are much richer in all digestive ferments than the digestive juices, and they contain them in active state. Periodical juices are much quicker absorbed from the empty intestine into the blood, than the digestive juices, which is quite natural and easily understood. The food in intestines binds ferments.

These very periodical juices, pancreatic and intestinal and their
ferments are the destructive forces which effect the autolysis of the liver cells in acute yellow atrophy of the liver.

In normal conditions these destructive ferments also reach the liver cells with the portal circulation. But then there is not so much of them and their potential harm is somehow prevented, they are rendered inactive.

Sometimes, however, for reasons unknown, the periodical activity is more pronounced and then the named ferments overflow in the portal circulation in enormous quantities in active state. By the way, our experiments show that this occurs in pregnancy. The organism tries to get rid of the excessive destroying ferments and throws them outside in vomiting (vomiting in the pregnant), but this measure is not always sufficient.

Then the liver comes back into its usual role of a barrier against poisons, coming from the intestine. Liver cells, in some unknown manner, bind up the ferments. We assume that there is some destruction of the liver cells, if the ferment action is excessively powerful when their quantity is especially great in the liver.

But if the liver is unable to hold all these active ferments, a part of them break into the general blood stream and cause destruction of the red blood corpuscles. Furthermore, the same ferments are responsible for the processes of degeneration in the muscles and in the kidneys which are observed in the acute yellow atrophy of the liver.

By their presence in the blood should be explained all other manifestations peculiar to this disease (brain changes, etc.). Then we have a clear picture of the disease. Also we understand the origin of the jaundice: 1. a portion of bile gets its way into the blood together with other periodical juices; 2. destruction of the red corpuscles* causes a hemolytic jaundice.

Now I must add that the periodical ferments are found in larger quantities in blood of women and their quantity in the intestine is particularly increased in pregnancy. Owing to these facts it becomes at once apparent why acute yellow atrophy of the liver is more frequent in women and most usually follows a pregnancy.

From this point of view it is not difficult to explain why a cirrhosis of the liver predisposes an individual to the disease we are now

* Our data show that there is such destruction in normal condition, on a small scale; then it has no harmful effect. But in this case is enormous in proportion to active destructive ferment entering the blood.
discussing. If the normal liver tissue can successfully combat over-
flowing periodical ferments, liver tissues, weakened by cirrhosis may
fail to do so.

Now we also understand the source of leucin in the blood and
urine, as well as tyrosin and other products of protein digestion which
are not normally found there in large quantities.

It is timely here to quote some data of our old and recent experi-
ments with the introduction of various digestive juices into the blood
of dogs.

Introduction of bile and zymogen pancreatic juice in one por-
tion about 30 cc. to dogs weighing about 15 to 20 kilos proved quite
harmless. But the same quantity of the active pancreatic juice, pour-
ed into the jugular vein of three healthy dogs, killed them all in about
24 hours, with identical symptoms of poisoning.

Symptoms of the acute yellow atrophy of the liver are similar
to those due to poisoning by phosphorus. Munk even believed that
all cases of this disease date back to a phosphorus poisoning.

If we admit that phosphorus, along with other poisonous irri-
tants of the mucous membrane of the intestine, causes an abundant
secretion of pancreatic juice into the intestine, we do understand the
likeness between the acute yellow atrophy of the liver and a phospho-
rus poisoning and it seems quite natural. Causes and mechanism
of both diseases are about the same with the only difference that in
the second instances there is an additional factor from the poison of
phosphorus itself.

Ferments which cause the acute yellow atrophy of the liver are
not generated inside its calls but are brought therein from the in-
testine with the blood of the portal vein. Therefore, owing to the
system of the blood vessels in the liver, these ferments first of all
reach the peripheral cells of each liver acinus and thus begins their
destructive work in the peripheral cells. Later the blood stream
comes to the inner parts of the acini and the process of their atrophy,
which is nothing else but their digestion, also occur later.

There would be no such regularity in the atrophy in this disease,
if the intracellular ferments or those contained in the bile were at
work instead of the ferments coming from outside.

* We must remember that the bile is either very poor in ferments or absolutely
free from them.
Treatment.

This disease has always been considered incurable and did not yield to any treatment.

But, assuming that we have discovered its cause, formerly unknown, we may now try a rational treatment with a certain hope for success.

It is apparent that the quantity of periodical ferments entering the portal vein should be diminished, since they enter the liver and injure it. In other words, we must lessen the periodical or other secretion in the pancreas, or at least temporarily lead it outside, not allow it to reach the diseased liver, in order to let this organ get some rest.

If we knew with certainty the cause or causes with increase and diminish the pancreatic secretion and if we knew how to check this secretion, all this would have been much simpler and much more dependable.

But we do not know what are the internal powers in the organism which regulate the periodical pancreatic secretion and therefore we cannot stop it directly. Moreover, thus stopping it for a long period would immediately involve diabetes, as proven by our experiments. Thus, we are here between two fires.

We know that pregnancy increases the periodical activity of the pancreas. Therefore when it is over this activity should be diminished and the symptoms of the acute yellow atrophy of the liver it produced would also abate. If the disease is not due to pregnancy, leading a portion of periodical pancreatic secretion outside (as it is done by the organism in vomiting), would be an important and beneficial measure of treatment.

Such drawing of secretion outside the patient’s body is simply affected through a temporary intestinal fistulae in duodenum, or better through duodenal tube. But there are other simpler methods not involving bleeding. We know that cold temperature increases periodical activity, and warmth decreases it. Then, we must do all we can to preserve the patient from cold and keep him warm all the time. I have observed complete stoppage of periodical activity in dogs during hot weather in the summer.

Keeping the patients in warm rooms with an even temperature is one of the best means of treatment.

One should think that prevention of the effect of cold and using
warm temperature would prove beneficial in prophylactic way, preventing development of the disease.

Contagious diseases and those accompanied by high temperature, increase the pancreatic secretion and thus predispose to contracting acute yellow atrophy of the liver.

Strenuous muscular exercise also produces this secretion, and for this reason patients who have acute yellow atrophy of the liver need complete bodily rest.

Other conditions productive of abundant pancreatic secretion are described in my article “Diabetes Mellitus and Its Treatment.”

If all this is correct, the acute yellow atrophy of the liver should be more frequent in the countries of cold climate and rarer in warm climate. Further statistics should prove the correctness of this conclusion.

Besides warmth there are other means of lessening secretions in general and pancreatic secretion in particular, such as atropin and other similar substances.

In treatment of the acute yellow atrophy of the liver one must strive to prevent excessive pancreatic ferments in the liver. Probably use of laxatives would be practical for this purpose, not all laxatives without discrimination, however, but only those which do not produce secretion of the pancreatic juice. There are very few of these, and bitter salts (for instance MgSO₄) and oils (castor oil, etc.) are powerful secretagogues for the pancreatic juice & are not suited. In this instance quite beneficial is the use of liquid paraffin and mucous substances. One must remember, however, that laxatives effect only a temporary relief, since our data show that absorption of pancreatic ferments takes place in the very beginning of the small intestine in a very short time. Use of mucous laxatives is good for mucus absorbs pancreatic ferments and carries them along outside the intestine. Kaolin or charcoal powder, and liquid egg white may be also used for the same purpose.

There is remaining one phenomenon which I cannot explain and that is the poor coagulability of blood in people suffering from the acute yellow atrophy of the liver. Our experiments have shown that blood coagulation is caused by the pancreatic ferment; it would appear that with excess of the pancreatic ferment in the blood its coagulation should not decrease but should be quicker. Perhaps, the cause of this slowing of coagulation is due to absence of some substance yielded by the normal liver into the blood and now insufficient
when the liver is weakened. Apparently this requires further study and investigation.

SUMMARY.

We have found on dogs that increased external secretion of the pancreatic juice may flood the liver with pancreatic ferments. These come there through vena portae. Overflooding of the liver with the pancreatic ferments may involve digestion of the specific liver cells causing acute yellow atrophy of the liver.

Conditions which are capable of increasing and decreasing the pancreatic secretion are described. Following these instruction one may prevent or arrest development of the atrophy of the liver.

These data are applicable to human patients in clinic for treatment of the acute yellow atrophy of the liver.

REFERENCES.

(3) Boldyreff, W.N.: Revista Pasteur, 1908.