TREATMENT OF EXPERIMENTAL HEPATIC INSUFFICIENCY WITH INTRAVENOUS INJECTIONS OF LIPOIDS *

By JUAN SURÓS FORNS, MORACHO and PASCUAL
Of the Medical Faculty of the University of Barcelona, Spain.**

The treatment of inflammatory diseases of the liver is not having the success to be desired.

We have often seen a fatal ending in patients who have been subjected to the only treatment at our disposal, namely, a hypotoxic diet and glucose, with or without insulin (as recommended by Richter and Umber). Substitution therapy, such as the administration of liver extracts parenterally, does not seem to influence favorably the regenerative properties of the hepatic parenchyma.

This preliminary paper to a more extensive work on the same subject deals with a new mode of therapy now being tested by us, experimentally and clinically, and on the success of which we are basing many hopes. We refer to the treatment of hepatic insufficiency by lecithin.

Notwithstanding the fact that Satta and Fassiani spoke of the action of the lipoids on autolysis of the liver, it is obvious that the American school of investigators must be given credit for being the first to point out the favorable action of lecithin, when given by mouth, on hepatic insufficiency. Some of those whose works along this line are recognized are Hershey [1], Best and Hershey [2], Best, Hershey and Huntsman [3], who have published their findings since 1930.

These investigators produced a condition of diabetes in dogs by pancreatectomy, and found that even under a sufficient diet (300 gms. of meat and 100 gms. of sugar) together with the necessary quantity of insulin to permit a light glycosuria, at the end of a certain time, varying between weeks and months, the disease would evidence itself in deficient hepatic function shown by asthenia, urobilinuria with choluria, moderate jaundice and intense wasting, which progressed in severity until the animal died in a comatose condition.

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This clinical picture was correlated with pathological findings of marked fatty infiltration of the liver.

Sandmeyer [4], who years previously had suspected this condition in his depancreatized dogs, found he could substantially improve their condition by feeding them with raw pancreas. According to this author, the symptoms of these animals were occasioned by a deficit of pancreatic secretion, or rather, a lesion of the hepatic organ caused by toxic digestive products produced by the lack of the said enzyme. Best and Hershey, furthering this experiment, also obtained an improved condition by substituting for the raw pancreas sufficient quantities of commercial lecithin administered by mouth. The anorexia and apathy became visibly ameliorated, the urobilinuria ceased and the cholemia disappeared. It was curious to note, after careful examination, that the sugar secreted in the urine increased as the hepatic function improved, as a result of the lecithin—we might say that there was aggravation of the diabetes as the hepatic insufficiency improved. Thus, Best, Hershey and colaborators observed that certain glycosurias, evidenced by 3 to 4 gms. elimination daily, rose to 15 gms. or higher. Needless to say, the tolerance of the individual towards insulin is greatly modified. Apropos of this, we have remarked that this relation between the tolerance for glucose in diabetes and hepatic insufficiency has also been clinically noted: Ercklentz [5] and Unger [6] observed that diabetics improved when hepatitis developed. It is a well-known fact that diabetics experience improvement in respect to glucose tolerance when chronic hepatopathy of cirrhotic type develops.

Also, we might mention here that the post lecithin glucosuria experienced by the experimental animals was not due to the transformation of the lecithin itself, nor to an increase of hepatic glycogenolisis, because the glycogen content of liver and muscles, after and before administration of the lecithin, does not undergo marked changes. For this reason, it (the post lecithin glycosuria) must be attributed to greater combustion of the fats stored in the liver. This hypothesis is borne out by the marked diminution of these substances by the action of lecithin. Worthy of note are the observations of Leathes [7], McLean and Bloor [8], who attribute to the phospholipins an important rôle in the desaturation and mobilization of the fats stored in the liver.

All these theories based on experimental observations have been adopted and tried out clinically, but with the exception of the works of Morawitz [9], Rosenthal [11], to whom Sala Roig [10] has referred in an interesting monograph, few are the authors, including those of the United States, who advocate this therapy.

We consider, however, that this therapy is capable of giving better results than are being obtained at present. In the first place, it is necessary to change its method of administration, and also, we consider it indispensible to take advantage of the action that the lipoids, especially the esters of cholesterin, exercise on the lecithin. The marked antagonism of lecithin toward cholesterol becomes a very desirable therapeutic action.

In the first place, the administration of lecithin, *per os,* is faulty technique, its utilization not always being secured, as other investigators have remarked from time to time.

Bokay [12], working in Strassburg in the laboratory of Hoppe-Seyler, showed decomposition of lecithin by the pancreatic juice. Glycerin-phosphoric acid, neurin and various fatty acids resulting from its decomposition, were in part used up by the organism. The others were eliminated by the digestive tract.

Politis [13], in a rather later work, demonstrated that lecithin was absorbed by the digestive organs only to the amount of 7.7 per cent. The 92.3 per cent remaining was disintegrated and reabsorbed, as could be proved by the secretion of phosphorus in the urine. Schoumoff-Limanowski and Sieber [25] observed the reduction of commercial lecithin, or of egg yolk, by the action of pancreatic juice. Cruto [14] in a reliable work, shows a quantity of trimethylamin and formic acid in the urine when lecithin is administered by mouth, an occurrence which is never so marked when administered by injections. We may state, then, definitely, contrary to the findings of Stassano and Billón [15], that lecithin, as such, is only utilized when it is administered parenterally (Serono [16] and Aducco [17]).

Lecithin isolated in suspension is difficult of usage, because it changes easily under the action of air and light. The secondary products caused by this change—choline, and especially lisolecithin—are easily productive of abscesses and general toxic manifestations, fever, convulsions, etc. Dani-

lewski [18] found this out, as the first author to investigate local effects of lecithin.

To make of lecithin a stable product susceptible to long conservation, it needs the presence of other lipoids, principally esters of cholesterol. Such a combination we find in egg yolk, lipoid emulsion to which we must resort when we desire to obtain this therapeutic preparation. Serono [19] was the first to record the influence of the cholesterol esters on the lecithin molecule, which they fix and surround with a protective colloid covering. Langue and Lawaczeh [20] observed that the oxidation of lecithin by ferric chloride is further retarded and even prevented by the addition of progressive quantities of cholesterol esters. The action of this last substance is not limited to the rôle of physical protection, but rather favorably modifies its therapeutic properties. Cruto [21] made a comparative study of the behavior of lecithinized rabbits and those submitted to the action of the lecithin plus the cholesterol esters. In these last, the weight curve took a sharper uptrend, and the quantity of hepatic glycogen was hardly changed, in contrast to the first which showed an intense diminution.

The preparations of lecithin plus esters of cholesterol, obtained, as we have said, from egg yolk, can be used intravenously with perfect ease, as Cruto [21] demonstrated in 1927. With such preparations, no sign of intolerance was observed, neither the acidosis which follows the intravenous injections of emulsified oil. The product is readily absorbed, according to Mannelli [22], by the cells of the reticulo-endothelial system, and—this is the cause of our investigations—by the hepatic cell, which evidences intense phagocytic properties. Ruffini [24] verified this after injecting rabbits with heavy doses of Bioplastina.*

We may, then, understand why the intravenous method of using the lecithin esters of cholesterol emulsion gives us a method possible of administrating lecithin, not only in a

* We have used Serono's Bioplastina in our investigations, as it contains all the properties necessary for the purpose. In this emulsion, obtained from egg yolk by that author's own technique, the lecithin is united with esters of cholesterol, forming a non-decomposing element, which is absorbed by the celular elements. According to the author, this procedure enables the introduction into the interior of the cell the lecithin in its full action, and also the vitamins as contained in the egg yolk, which the pure lecithin lacks. This claim is supported by the observations of Hershey, who noted symptoms of avitaminosis in his dogs, which was not observed by Serono and Montezemolo [24] who used the intravenous method.

sufficient quantity, but as a lecithin molecule. Happy association with cholesterol makes it possible for us to obtain from lecithin its full therapeutic action.

From our experience to date we may deduce that the favorable effect obtained by Hershey when employing this material in hepatic insufficiency can be enhanced by parenteral administration. As lecithin alone cannot be used, owing to the difficulty of preserving it, and also because it produces secondary unfavorable reactions (decrease of hepatic glycogen, increase of metabolism), we should definitely employ preparations of egg yolk in which the different lipoids complement each other. For this reason, instead of using lecithin *per os* in the treatment of hepatic insufficiency, we recommend as a tested method the intravenous administration in the form of lecithin esters of cholesterol emulsion, which, as we have already said, permits us to obtain the freest therapeutic action.

To satisfy ourselves we undertook a short series of investigations, some experimental, some clinical. The first were conducted in the Institute of Physiology of the Faculty of Medicine of Barcelona where, assisted by the professors Pi Suñer and Bellido, we found all facilities possible. We were also grateful for the assistance rendered by Dr. Griera, intern.

The procedure was as follows:

A certain number of rabbits, four months old, and of the same litter, was divided into groups. Each one was injected on alternate days with phosphorated oil in amount of 0.5 mg. of phosphorus per kilo of body weight. The first two rabbits were given simultaneously on alternate days an intravenous injection of 5 cc. of an emulsion of lecithin esters of cholesterol. In the second group this was administered by the gastric route (by tube) to the amount of 1 gm. per day; the two remaining rabbits took only phosphorated oil with no lecithin.

All of them were weighed weekly, and tests were made for bilirubinemia, which enabled us to keep track of hepatic functioning. These determinations have been made by Dr. Agustí Coranti, using Pulfrich's refractometer, and Jendrasik and Czike's technique. With the data thus obtained we have constructed chart 1, which is self-explanatory. It demonstrates how in the rabbits given phosphorus alone, or phos-

phorus plus lecithin by mouth, the bilirubin rapidly ascended in a similar manner in all of them. The survival time of three weeks in rabbit 1, reached five weeks in rabbit 4, which was fed with lecithin by mouth. The remaining animals died four weeks after having been injected with the phosphorus. All rabbits gained weight—especially those receiving toxin alone.

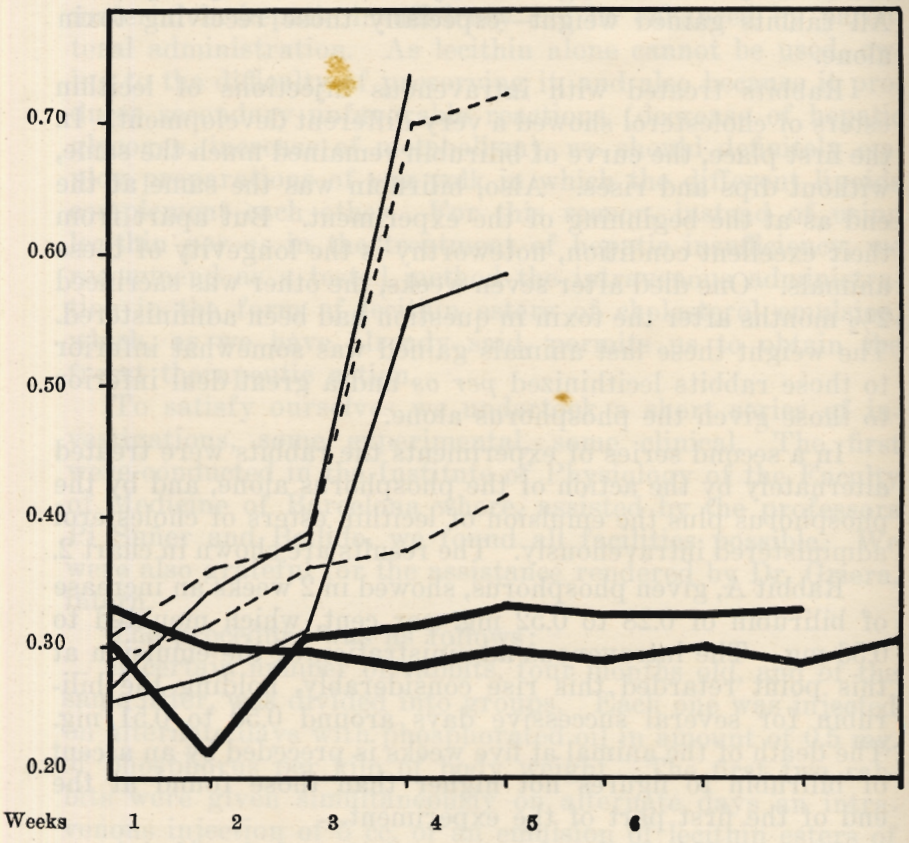
Rabbits treated with intravenous injections of lecithin esters of cholesterol showed a very different development. In the first place, the curve of bilirubin remained much the same, without dips and rises. Also, bilirubin was the same at the end as at the beginning of the experiment. But apart from their excellent condition, noteworthy is the longevity of these animals. One died after seven weeks, the other was sacrificed 2½ months after the toxin in question had been administered. The weight these last animals gained was somewhat inferior to those rabbits lecithinized *per os* and a great deal inferior to those given the phosphorus alone.

In a second series of experiments the rabbits were treated alternately by the action of the phosphorus alone, and by the phosphorus plus the emulsion of lecithin esters of cholesterol administered intravenously. The results are shown in chart 2.

Rabbit A, given phosphorus, showed in 2 weeks an increase of bilirubin of 0.28 to 0.52 mg. per cent, which mounted to 0.56 mg. The intravenous administration of the emulsion at this point retarded this rise considerably, holding the bilirubin for several successive days around 0.50 to 0.51 mg. The death of the animal at five weeks is preceded by an ascent of bilirubin to figures not higher than those found at the end of the first part of the experiment.

In the rabbit B the rise was to 0.49, and the administration of the emulsion from this point kept the amount of bilirubin steady. The death of the rabbit was also preceded by an intense rise of bilirubin. Rabbit C behaved differently: from the beginning, the emulsion was useless, failing to check the rise of the bilirubin and the cessation of the emulsion showed little influence over the bilirubinemia which continued to increase gradually.

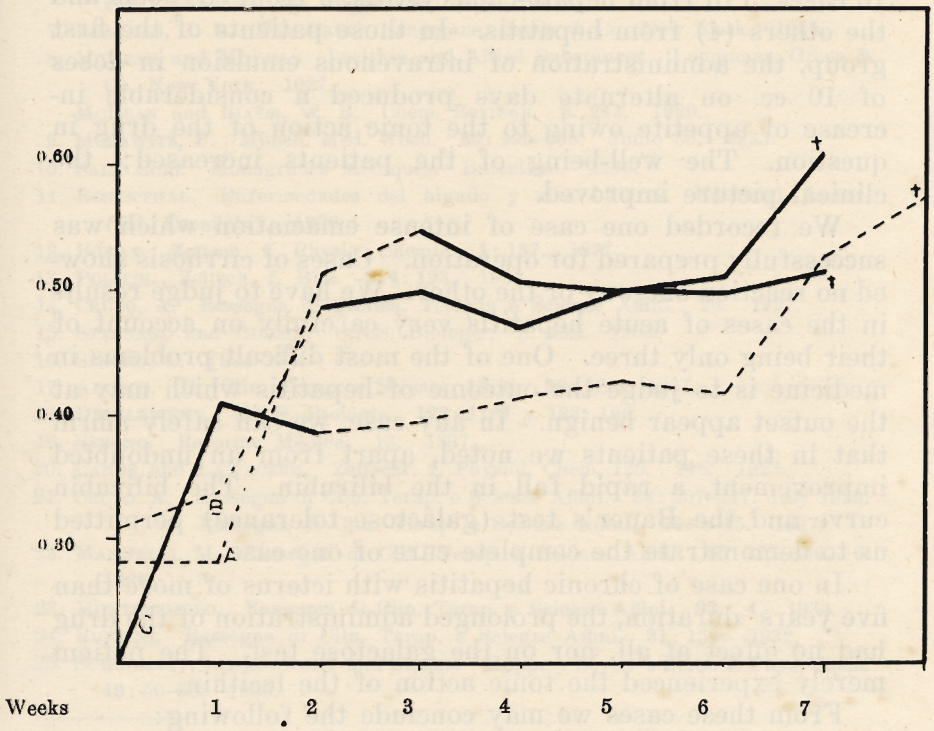
From this we may conclude that emulsion of lecithin administered intravenously ameliorates to a marked degree the hepatic insufficiency in rabbits subjected to the toxic action



GRAPH 1

Bilirubinemia curve trend in different rabbits.

——————— Rabbits injected intravenously with lecithin emulsion.
- - - - - - - - - Rabbits given lecithin by mouth.
——————— Rabbits given phosphorus only.



GRAPH 2

Trend of bilirubinemia curve in rabbits given alternatingly phosphorus and phosphorus plus emulsion of lecithin esters of cholesterol intravenously.

of phosphorus. The administration of lecithin by mouth appeared to us to be a less effective method.

The clinical tests took place in the majority of cases in the clinic of Dr. A. Pedro Pons, and cannot be considered of great significance on account of the few cases studied. However, it is logical to suppose that these preliminary observations are of value for reference when further studies on this subject shall be made. The treatment has been tried out in 10 cases, 3 ill from hepato-cholecystitis, 3 from cirrhosis and the others (4) from hepatitis. In those patients of the first group, the administration of intravenous emulsion in doses of 10 cc. on alternate days produced a considerable increase of appetite owing to the tonic action of the drug in question. The well-being of the patients increased; the clinical picture improved.

We recorded one case of intense emaciation which was successfully prepared for operation. Cases of cirrhosis showed no reaction one way or the other. We have to judge results in the cases of acute hepatitis very carefully on account of their being only three. One of the most difficult problems in medicine is to judge the outcome of hepatitis which may at the outset appear benign. In any case, we can safely affirm that in these patients we noted, apart from an undoubted improvement, a rapid fall in the bilirubin. The bilirubin curve and the Bauer's test (galactose tolerance) permitted us to demonstrate the complete cure of one case.

In one case of chronic hepatitis with icterus of more than five years' duration, the prolonged administration of the drug had no effect at all, nor on the galactose test. The patient merely experienced the tonic action of the lecithin.

From these cases we may conclude the following:

a. Those few patients studied suffering from liver disease presented an absolute tolerance towards intravenous injections of an emulsion of lecithin and esters of cholesterol. In no case have we observed the slightest set-back.

b. The tonic action of this drug helps improve the nutrition of the patient.

c. It appears to be an effective auxiliary to treatment in cases of acute hepatitis.

These clinical investigations are preliminary to further studies.

Trans. J. A. Pons and C. M. Locke.

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* NOTE: Owing to prevailing conditions in Spain, the Bibliography stands as received by the P. R. Jour. of Pub. Health & Trop. Med., without authors' revision.